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## Scientific and Technical Information Center

## SEARCH REQUEST FORM

Requester's Full Name: MARK BERCH Examiner #: 59193 Date: 6/13/07  
 Art Unit: 1624 Phone Number: 2-0663 Serial Number: 1053383  
 Location (Bldg/Room#): 5C01 (Mailbox #): 5C18 Results Format Preferred (circle): PAPER DISK  
 \*\*\*\*\*

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

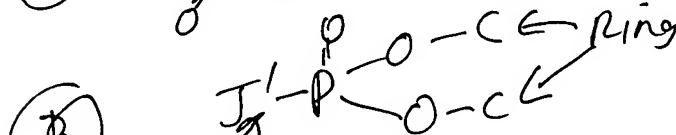
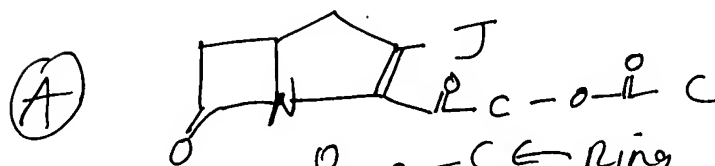
Earliest Priority Date: \_\_\_\_\_

## Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

CAS React



J, J' = Hal/O/S/N

Search A + B

done  
incase  
Fin 1 comp is  
not indexed as  
such in ref

## STAFF USE ONLY

Searcher: \_\_\_\_\_

Searcher Phone #: \_\_\_\_\_

Searcher Location: \_\_\_\_\_

Date Searcher Picked Up: \_\_\_\_\_

Date Completed: \_\_\_\_\_

Searcher Prep & Review Time: \_\_\_\_\_

Online Time: \_\_\_\_\_

## Type of Search

\_\_\_\_ NA Sequence (#)

\_\_\_\_ AA Sequence (#)

\_\_\_\_ Structure (#)

\_\_\_\_ Bibliographic

\_\_\_\_ Litigation

\_\_\_\_ Fulltext

\_\_\_\_ Other

## Vendors and cost where applicable

\_\_\_\_ STN \_\_\_\_\_ Dialog

\_\_\_\_ Questel/Orbit \_\_\_\_\_ Lexis/Nexis

\_\_\_\_ Westlaw \_\_\_\_\_ WWW/Internet

\_\_\_\_ In-house sequence systems

\_\_\_\_ Commercial \_\_\_\_\_ Oligomer \_\_\_\_\_ Score/Length  
 \_\_\_\_ Interference \_\_\_\_\_ SPDI \_\_\_\_\_ Encod/Transl  
 \_\_\_\_ Other (specify)

=> fil casreact  
 FILE 'CASREACT' ENTERED AT 09:25:59 ON 15 JUN 2007  
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FILE CONTENT:1840 - 9 Jun 2007 VOL 146 ISS 25

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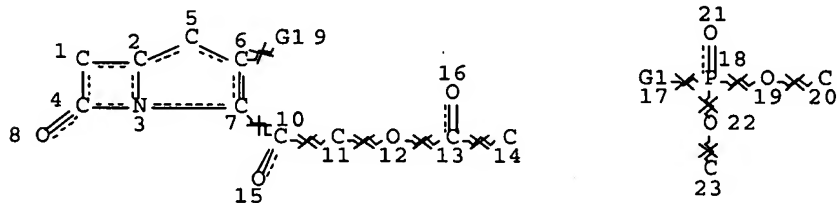
\*\*\*\*\*  
 \*  
 \* CASREACT now has more than 12 million reactions \*  
 \*  
 \*\*\*\*\*

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que 13

L1 STR



VAR G1=X/O/S/N

NODE ATTRIBUTES:

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NSPEC IS R AT 23

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

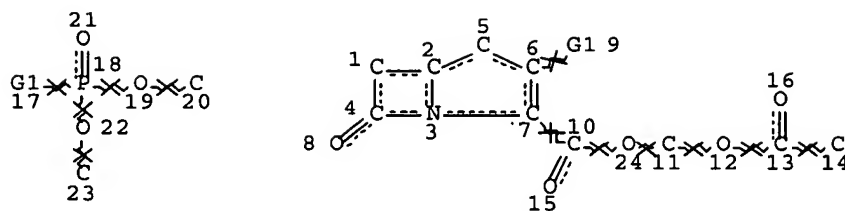
NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE

L3 0 SEA FILE=CASREACT SSS FUL L1 ( 0 REACTIONS)

=> d que 18

L6 STR



VAR G1=X/O/S/N

NODE ATTRIBUTES:

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NSPEC IS R AT 23

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

L8 4 SEA FILE=CASREACT SSS FUL L6 ( 90 REACTIONS)

=> d 18 ibib abs crd tot

L8 ANSWER 1 OF 4 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 145:335815 CASREACT Full-text

TITLE: Syntheses and pharmacokinetic studies of prodrug esters for the development of oral carbapenem, L-084

AUTHOR(S): Isoda, Takeshi; Ushiroguchi, Hideki; Satoh, Koichi; Takasaki, Tsuyoshi; Yamamura, Itsuki; Sato, Chisato; Mihira, Ado; Abe, Takao; Tamai, Satoshi; Yamamoto, Shigeki; Kumagai, Toshio; Nagao, Yoshimitsu

CORPORATE SOURCE: Medical Research Laboratories, Wyeth K.K., 1-6-34 Kashiwa-cho, Shiki-shi, Saitama, 353-8511, Japan

SOURCE: Journal of Antibiotics (2006), 59(4), 241-247

CODEN: JANTAJ; ISSN: 0021-8820

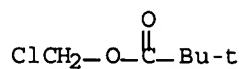
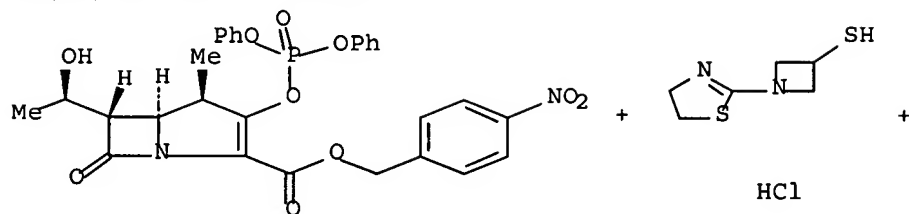
PUBLISHER: Japan Antibiotics Research Association

DOCUMENT TYPE: Journal

LANGUAGE: English

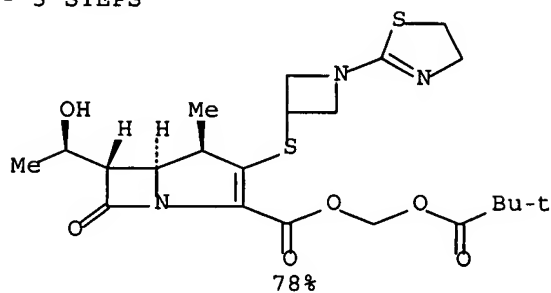
AB We discovered an orally active carbapenem, L-084, through pharmacokinetic studies on various prodrug esters of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[1-(1,3-thiazolin-2-yl)azetidin-3-yl]thio-1-carbapen-2-em-3-carboxylic acid (LJC11,036). L-084 showed a strong antimicrobial activity against Gram-pos. and Gram-neg. bacteria and exhibited the highest intestinal absorption among synthesized prodrugs of LJC11,036.

RX(38) OF 126 - 3 STEPS



- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. ~~PhCH2NEt3, Cl~~ →
- EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

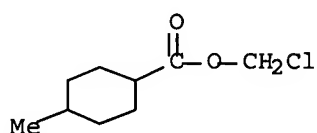
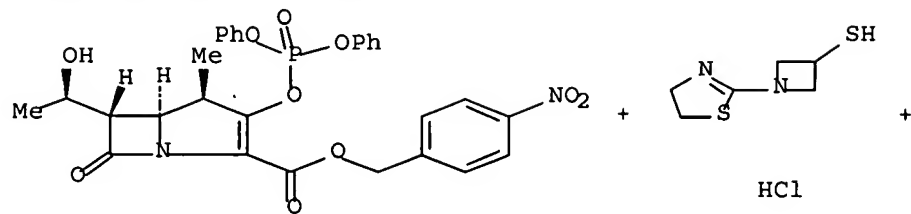
RX(38) OF 126 - 3 STEPS



78%

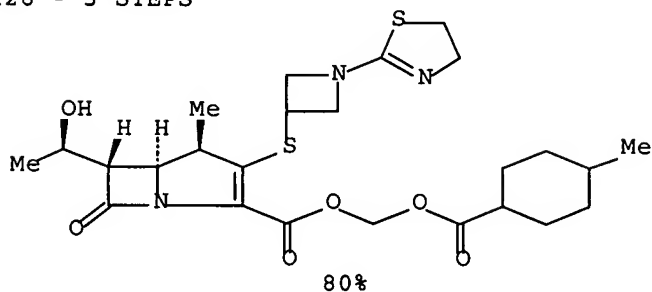
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(39) OF 126 - 3 STEPS



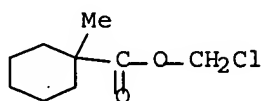
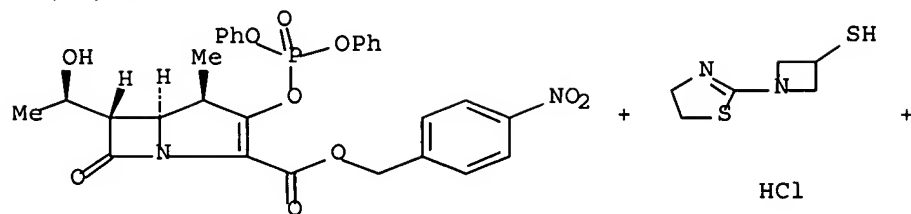
- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH2NEt3, Cl, EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

RX(39) OF 126 - 3 STEPS



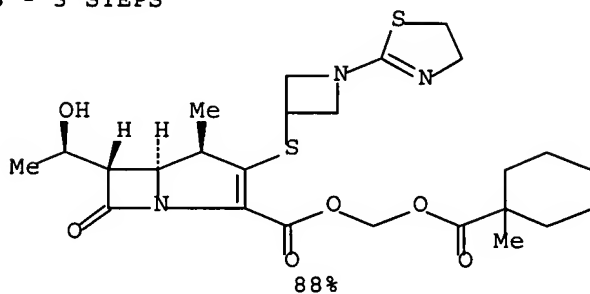
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(41) OF 126 - 3 STEPS



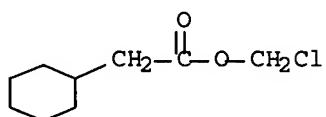
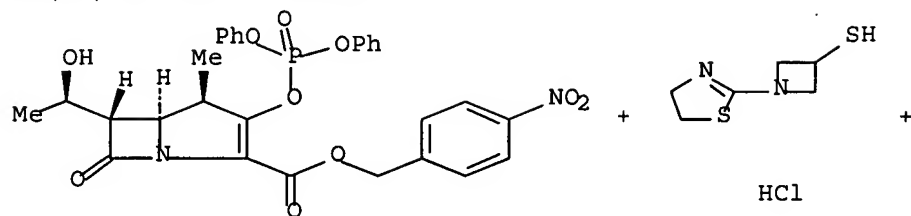
- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH2NEt3, Cl, EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

RX(41) OF 126 - 3 STEPS



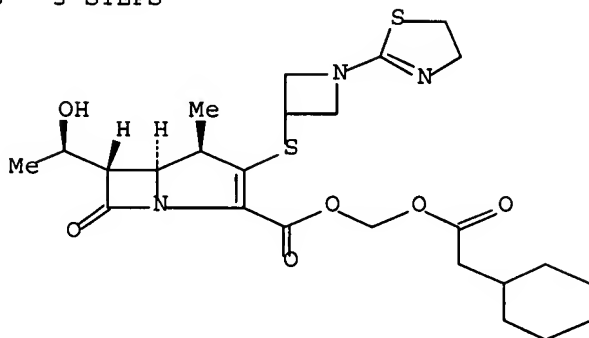
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(42) OF 126 - 3 STEPS



- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH2NEt3, Cl, EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

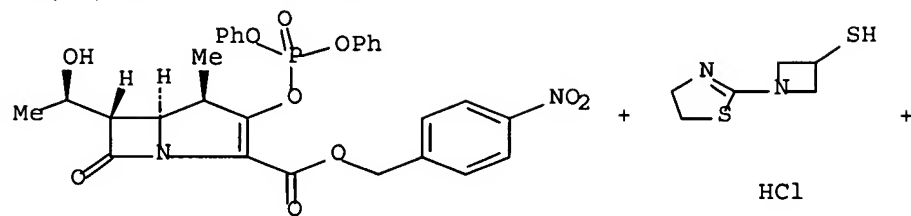
RX(42) OF 126 - 3 STEPS



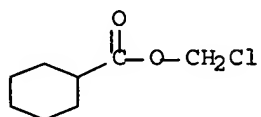
76%

CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(43) OF 126 - 3 STEPS

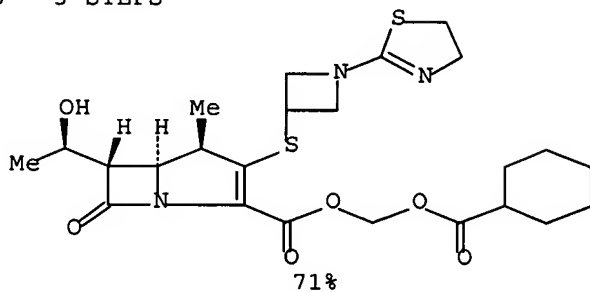


HCl



- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH2NEt3, Cl, EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

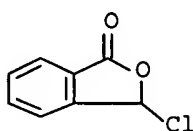
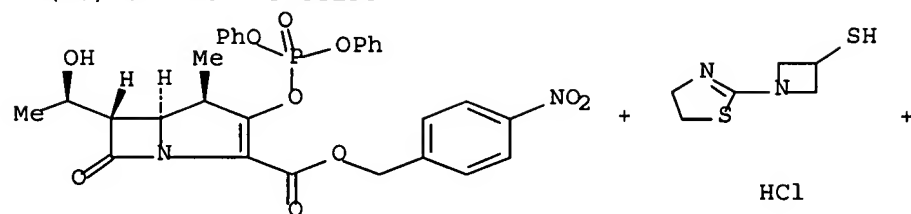
RX(43) OF 126 - 3 STEPS



71%

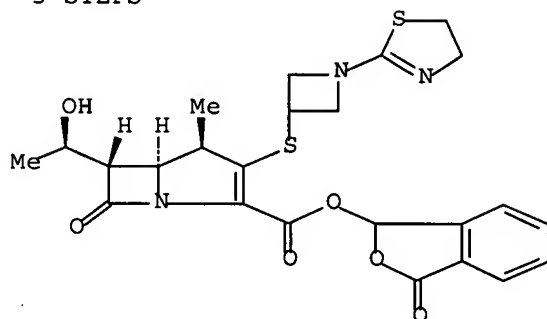
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(45) OF 126 - 3 STEPS



- 1.1. EtN(Pr-i)<sub>2</sub>, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO<sub>3</sub>, H<sub>2</sub>,  
Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH<sub>2</sub>NEt<sub>3</sub> Cl, EtN(Pr-i)<sub>2</sub>, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO<sub>3</sub>

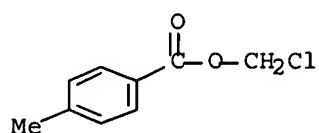
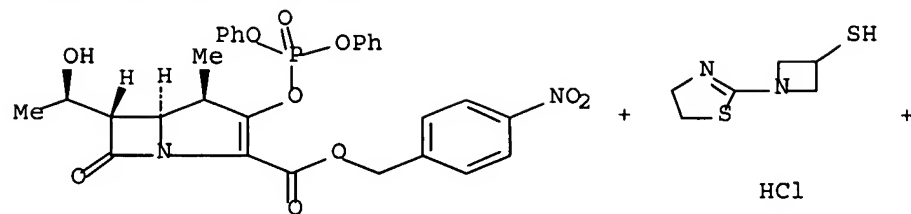
RX(45) OF 126 - 3 STEPS



84%

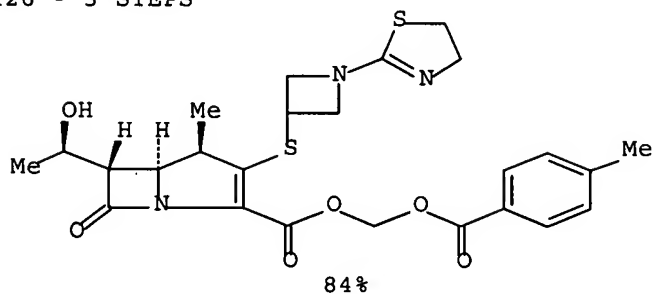
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(46) OF 126 - 3 STEPS



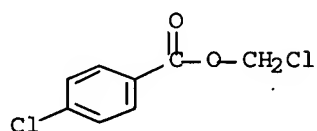
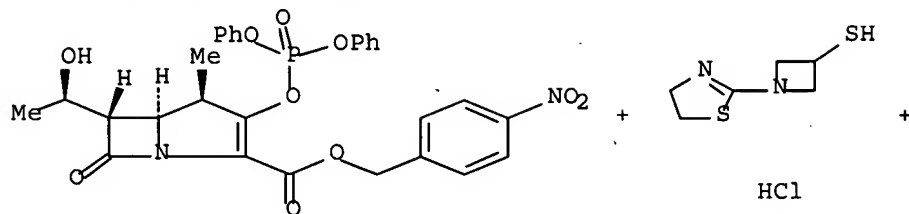
- 1.1. EtN(Pr-i)<sub>2</sub>, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO<sub>3</sub>, H<sub>2</sub>, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH<sub>2</sub>NEt<sub>3</sub> Cl, EtN(Pr-i)<sub>2</sub>, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO<sub>3</sub>

RX(46) OF 126 - 3 STEPS



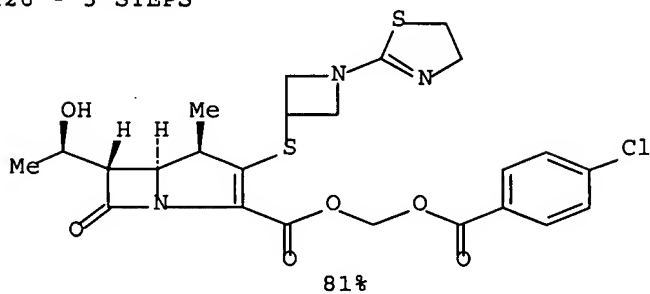
CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(47) OF 126 - 3 STEPS



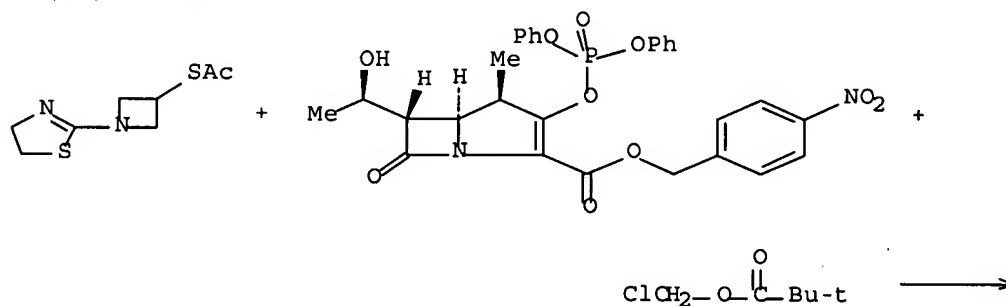
- 1.1. EtN(Pr-i)2, MeCN
- 1.2. Water
- 2.1. Pd, NaHCO3, H2, Water, BuOH
- 2.2. HCl, Water
- 3.1. PhCH2NEt3, Cl, EtN(Pr-i)2, DMF
- 3.2. Citric acid, Water, AcOEt
- 3.3. KHCO3

RX(47) OF 126 - 3 STEPS

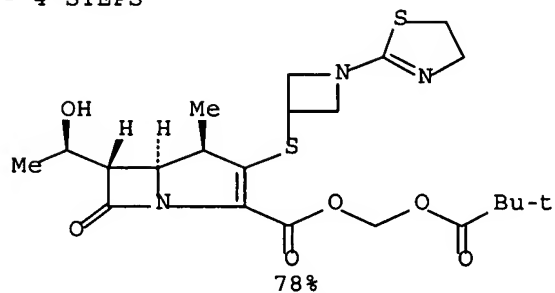


CON: STEP(1.1) 2 hours, -20 deg C  
 STEP(1.2) 0.5 hours, 5 deg C  
 STEP(2.1) 1.5 hours, room temperature, 400 kPa  
 STEP(2.2) pH 5.6  
 STEP(3.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(3.2) 5 deg C, pH 4  
 STEP(3.3) pH 7.6

RX(48) OF 126 - 4 STEPS

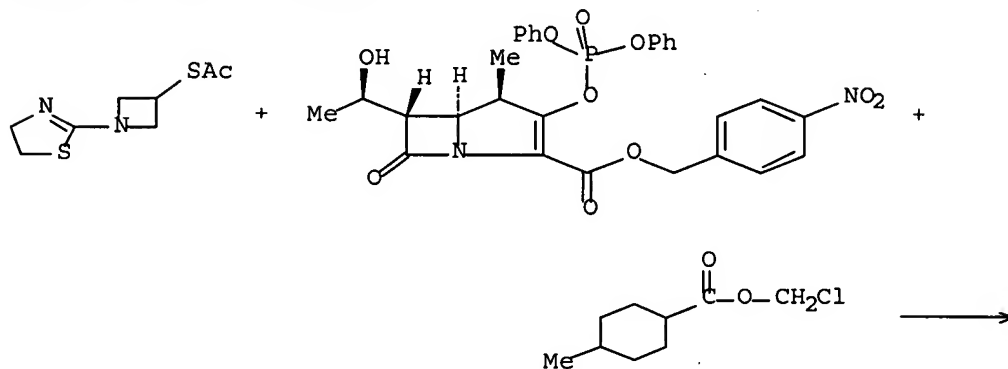


RX(48) OF 126 - 4 STEPS

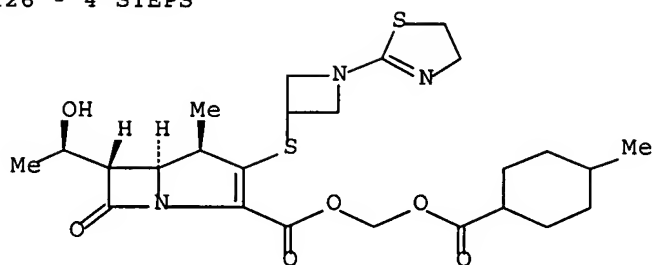


CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(49) OF 126 - 4 STEPS



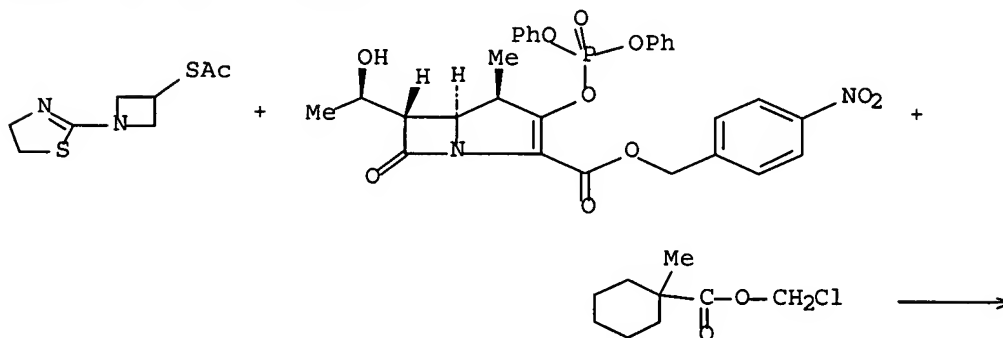
RX(49) OF 126 - 4 STEPS



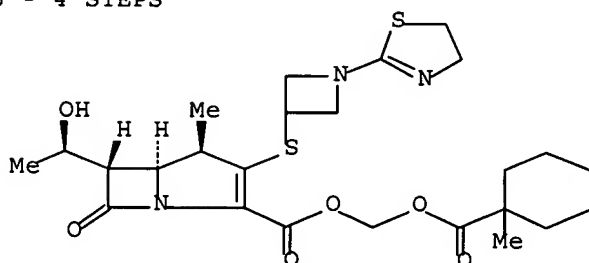
80%

CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(51) OF 126 - 4 STEPS



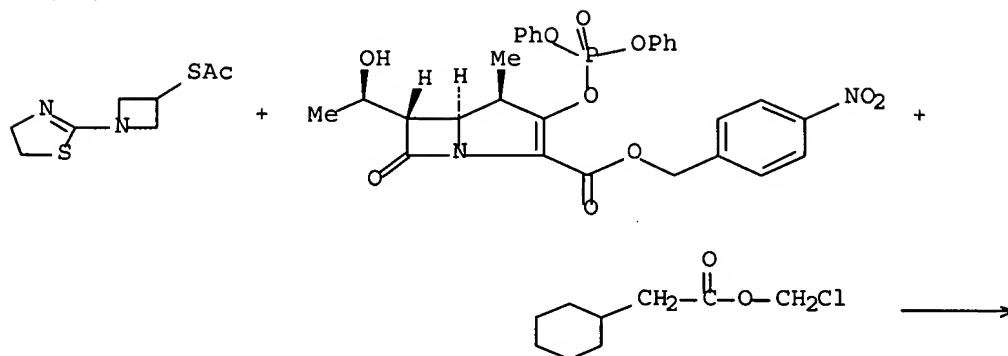
RX(51) OF 126 - 4 STEPS



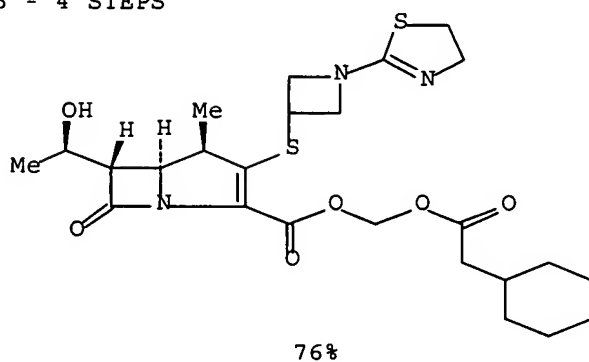
88%

CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(52) OF 126 - 4 STEPS

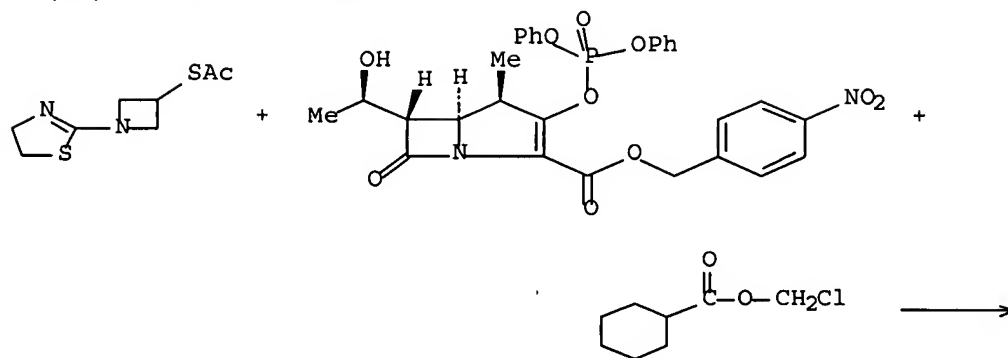


RX(52) OF 126 - 4 STEPS

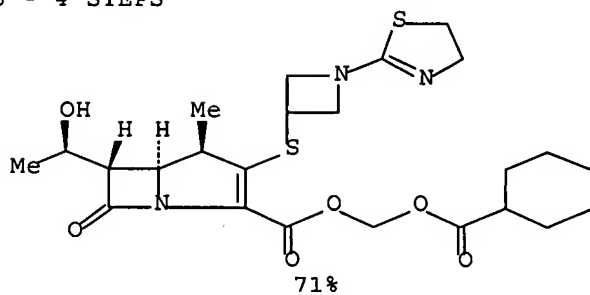


CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(53) OF 126 - 4 STEPS

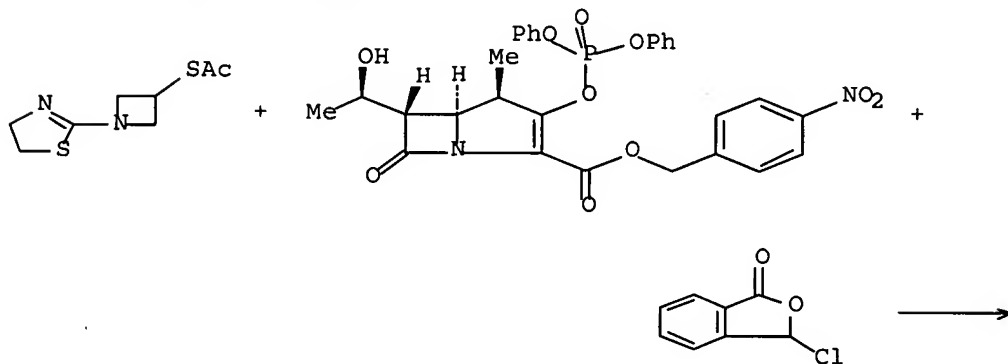


RX(53) OF 126 - 4 STEPS

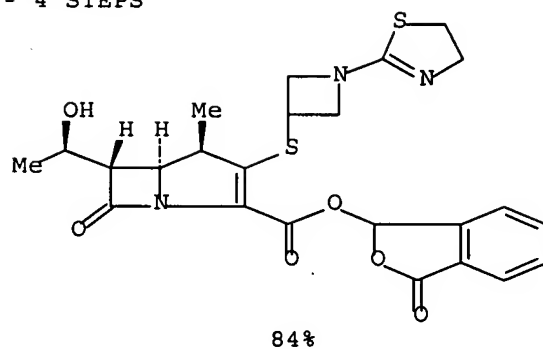


CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(55) OF 126 - 4 STEPS

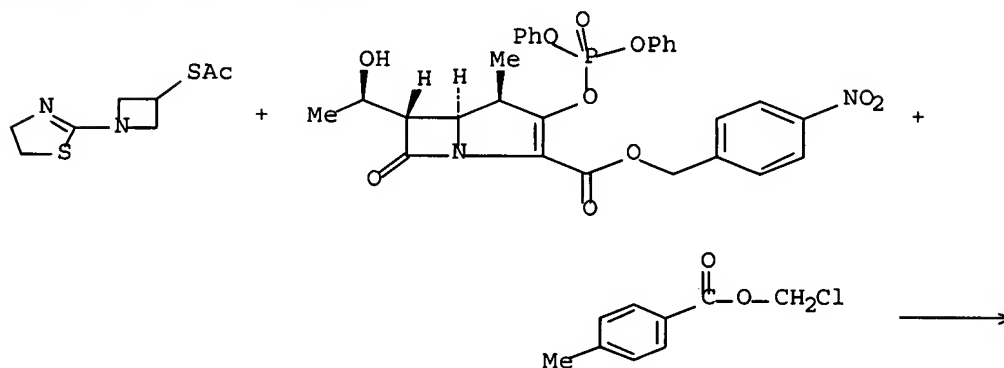


RX(55) OF 126 - 4 STEPS

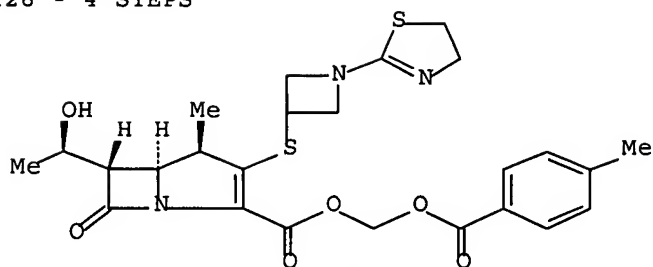


CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(56) OF 126 - 4 STEPS



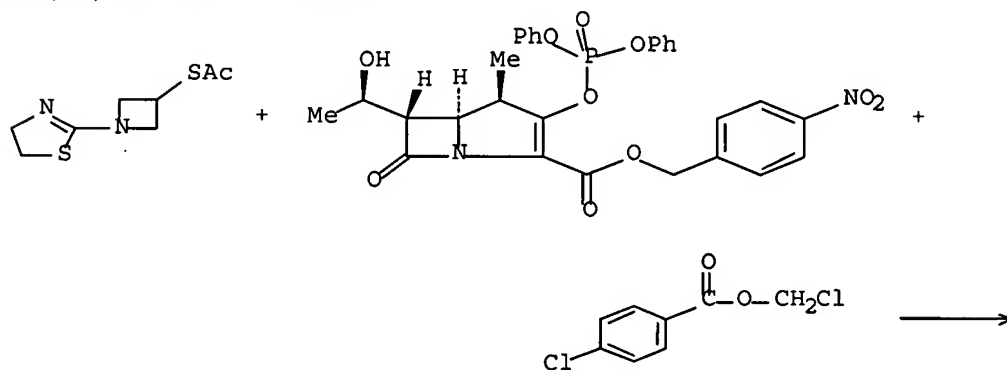
RX(56) OF 126 - 4 STEPS



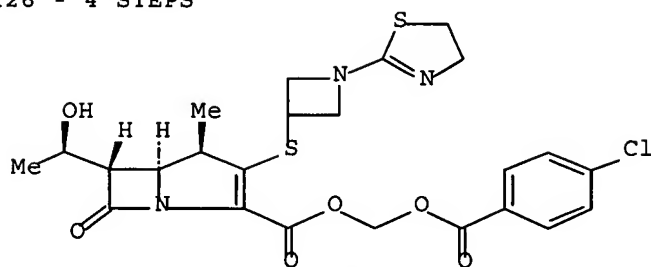
84%

CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(57) OF 126 - 4 STEPS



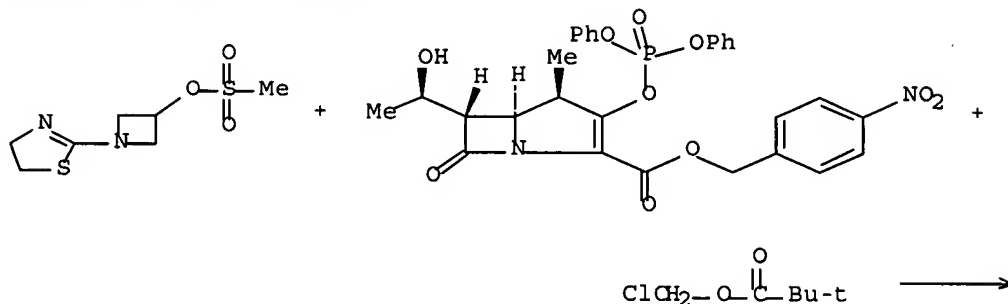
RX(57) OF 126 - 4 STEPS



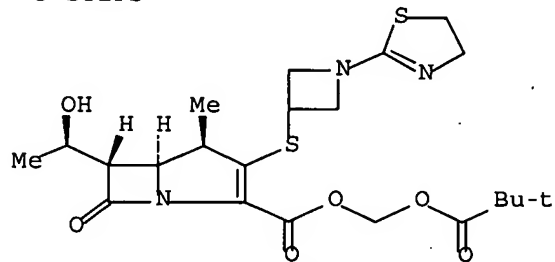
81%

CON: STEP(1.1) 10 minutes, 5 deg C  
 STEP(1.2) 15 minutes  
 STEP(2.1) 2 hours, -20 deg C  
 STEP(2.2) 0.5 hours, 5 deg C  
 STEP(3.1) 1.5 hours, room temperature, 400 kPa  
 STEP(3.2) pH 5.6  
 STEP(4.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(4.2) 5 deg C, pH 4  
 STEP(4.3) pH 7.6

RX(67) OF 126 - 5 STEPS



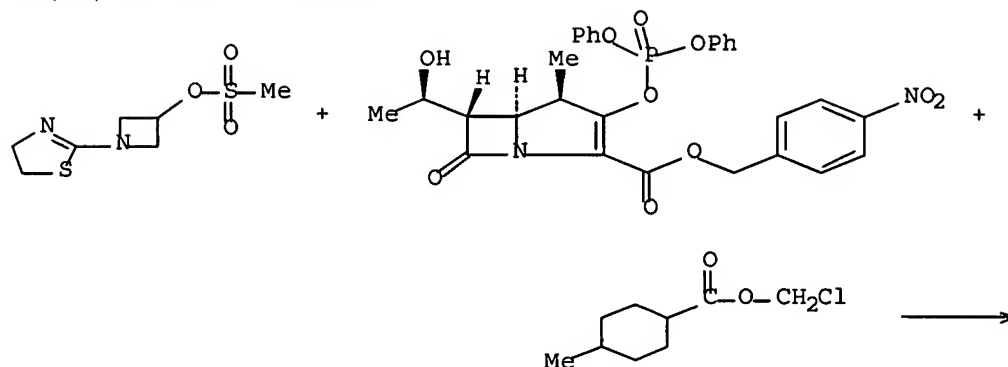
RX(67) OF 126 - 5 STEPS



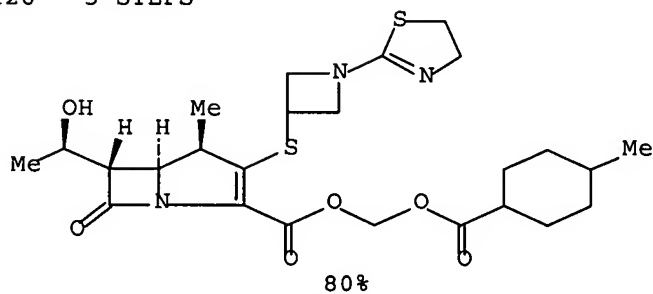
78%

CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(68) OF 126 - 5 STEPS

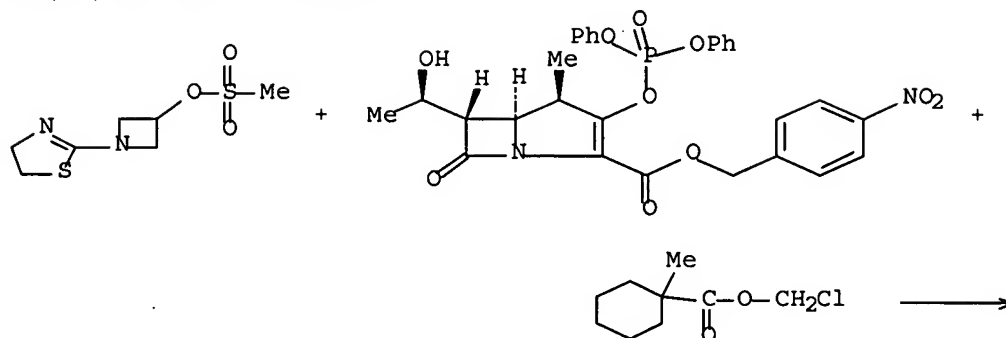


RX(68) OF 126 - 5 STEPS

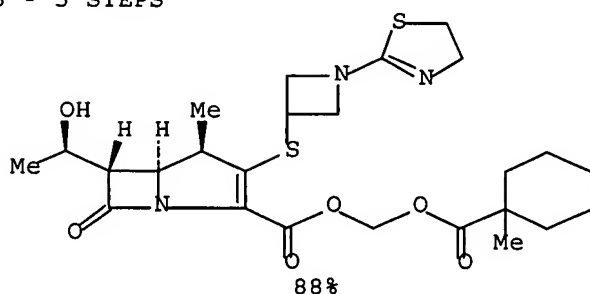


CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(70) OF 126 - 5 STEPS

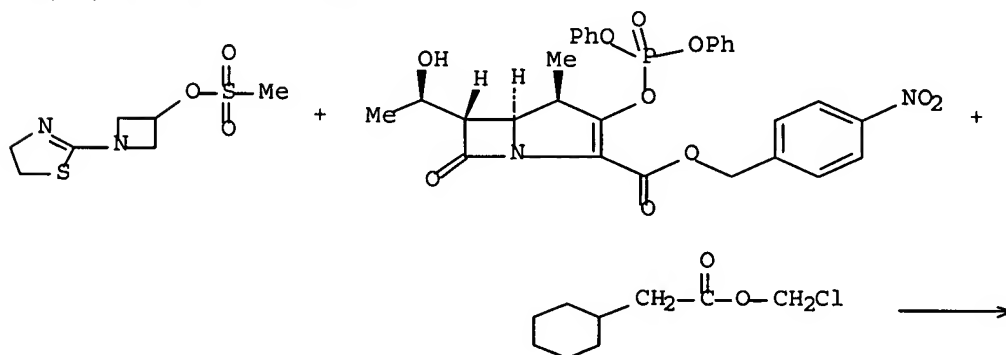


RX(70) OF 126 - 5 STEPS



CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(71) OF 126 - 5 STEPS



CC1(C)C(=O)N2C(=C(C(=O)OCCOC(=O)CC3CCCCC3)C=C(C2)SC4CCN(C4)C5=NC=CC=C5)C(C1)C

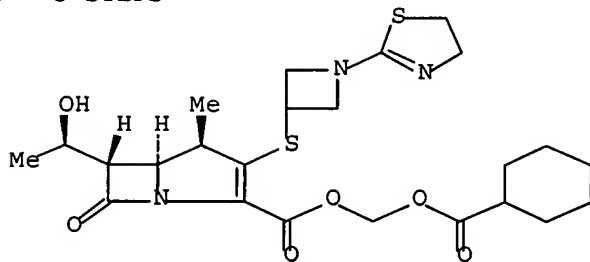
```

CON:  STEP(1) 5.5 hours, 100 deg C
      STEP(2.1) 10 minutes, 5 deg C
      STEP(2.2) 15 minutes
      STEP(3.1) 2 hours, -20 deg C
      STEP(3.2) 0.5 hours, 5 deg C
      STEP(4.1) 1.5 hours, room temperature, 400 kPa
      STEP(4.2) pH 5.6
      STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C
      STEP(5.2) 5 deg C, pH 4
      STEP(5.3) pH 7.6

```

CN1CC1S2CCN2C(=O)OC(=O)C + COC(=O)C1=CC=C(C=C1)[N+](=O)[O-] + ClCCOC(=O)C2CCCCC2 >> COC(=O)C1=CC=C(C=C1)[N+](=O)[O-]C(=O)C2=CC=C(C=C2)C3=C(C)C(=O)N(C3)C(=O)C[C@H](C)[C@@H](O)C + CN1CC1S2CCN2C(=O)OC(=O)C

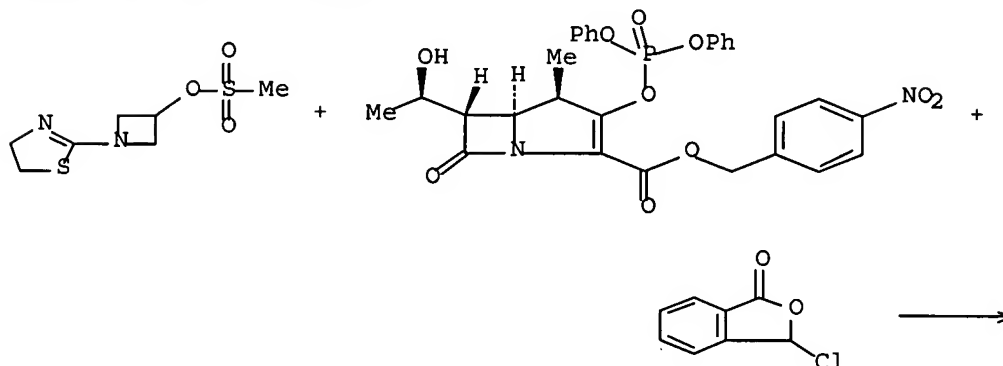
RX(72) OF 126 - 5 STEPS



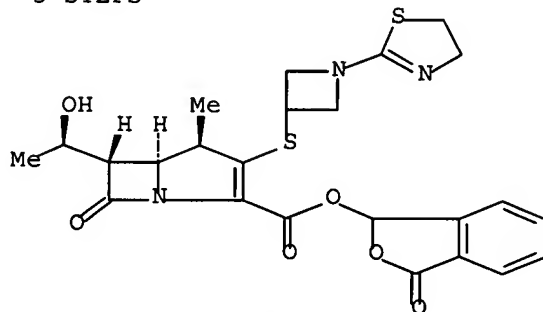
71%

CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(74) OF 126 - 5 STEPS



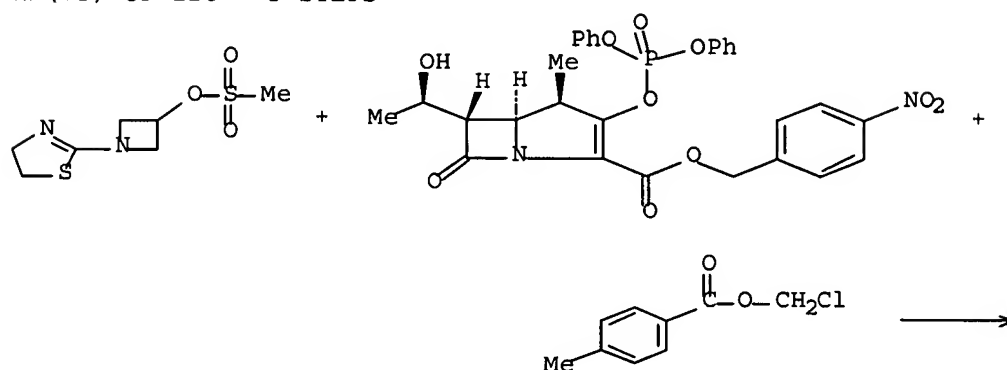
RX(74) OF 126 - 5 STEPS



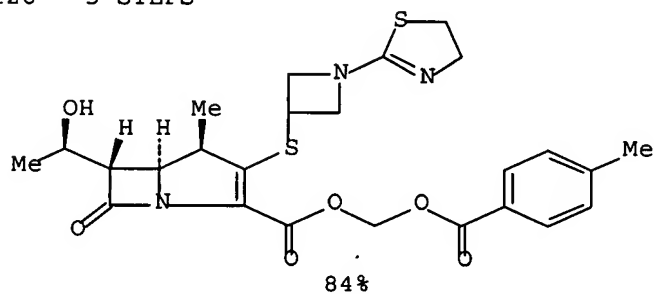
84%

CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(75) OF 126 - 5 STEPS

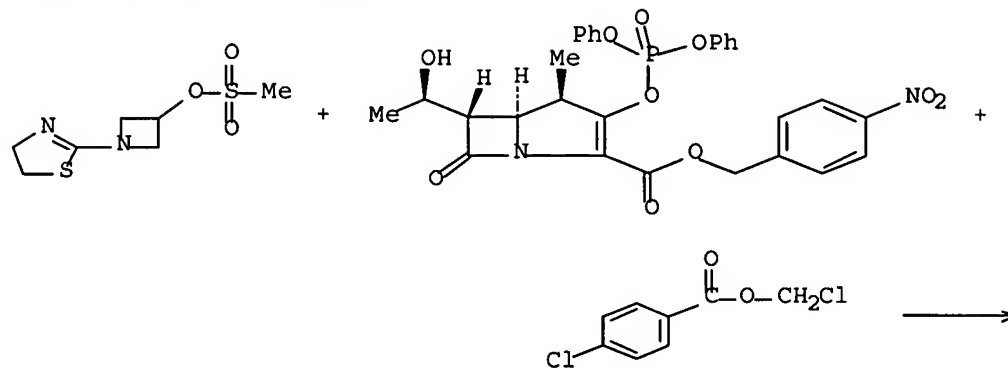


RX(75) OF 126 - 5 STEPS

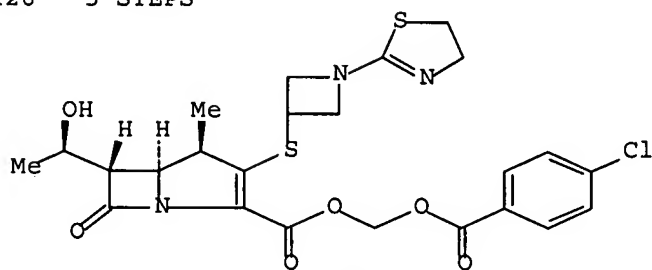


CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(76) OF 126 - 5 STEPS



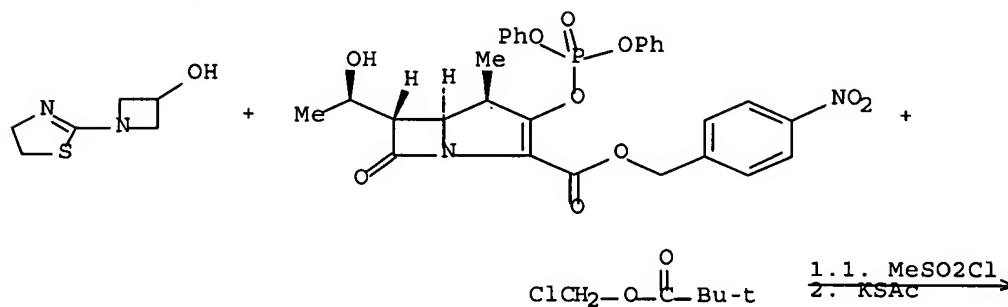
RX(76) OF 126 - 5 STEPS



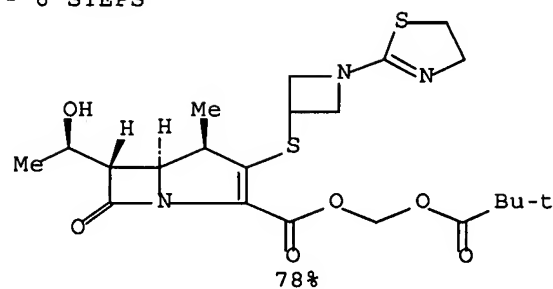
81%

CON: STEP(1) 5.5 hours, 100 deg C  
 STEP(2.1) 10 minutes, 5 deg C  
 STEP(2.2) 15 minutes  
 STEP(3.1) 2 hours, -20 deg C  
 STEP(3.2) 0.5 hours, 5 deg C  
 STEP(4.1) 1.5 hours, room temperature, 400 kPa  
 STEP(4.2) pH 5.6  
 STEP(5.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(5.2) 5 deg C, pH 4  
 STEP(5.3) pH 7.6

RX(77) OF 126 - 6 STEPS

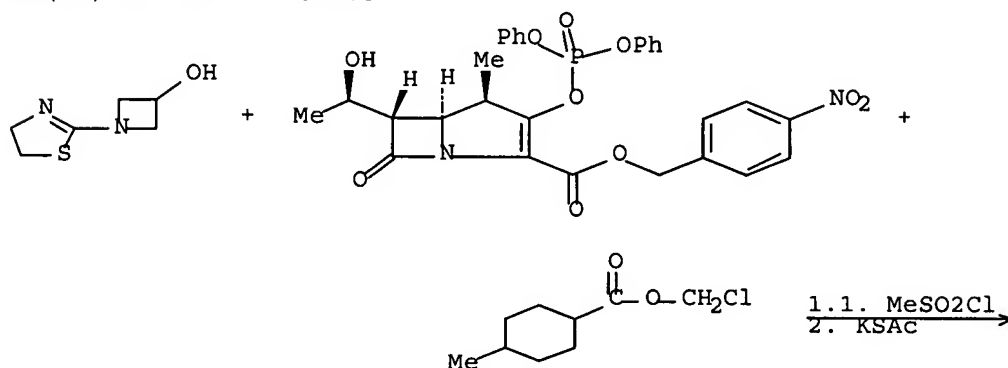


RX(77) OF 126 - 6 STEPS

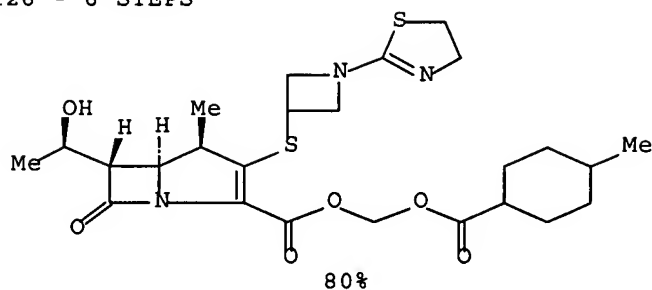


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(78) OF 126 - 6 STEPS

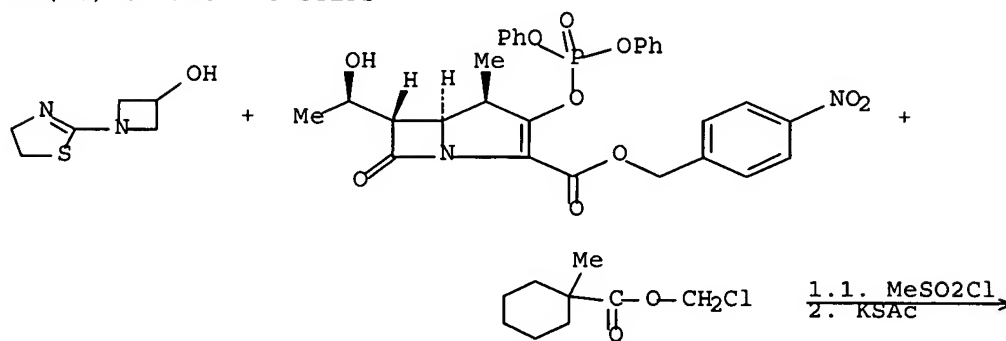


RX(78) OF 126 - 6 STEPS

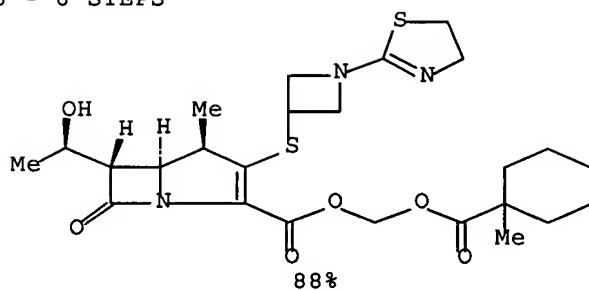


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(80) OF 126 - 6 STEPS

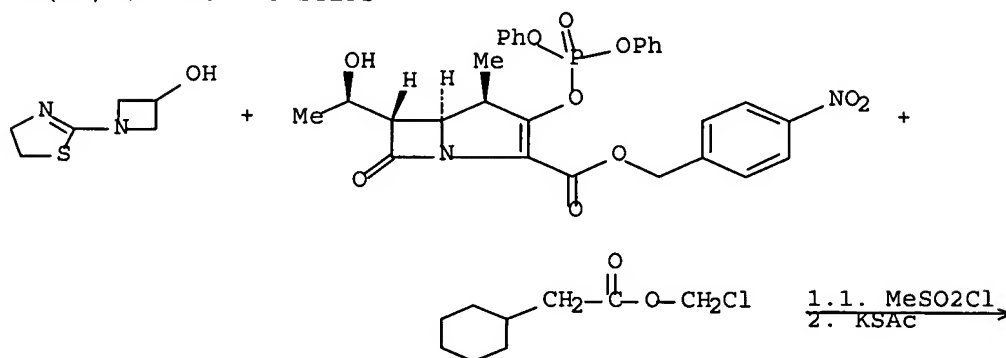


RX(80) OF 126 - 6 STEPS

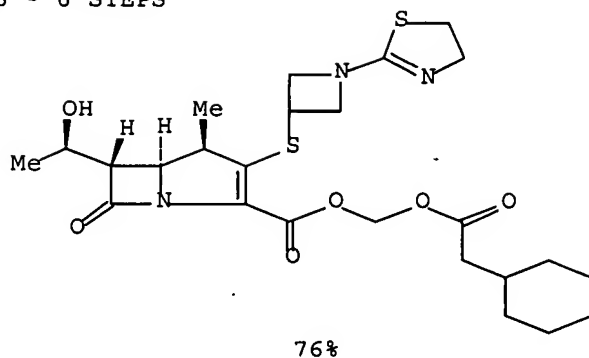


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(81) OF 126 - 6 STEPS

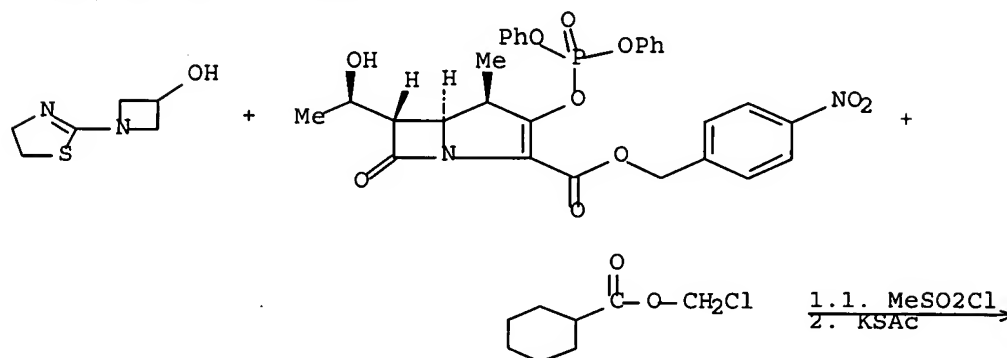


RX(81) OF 126 - 6 STEPS

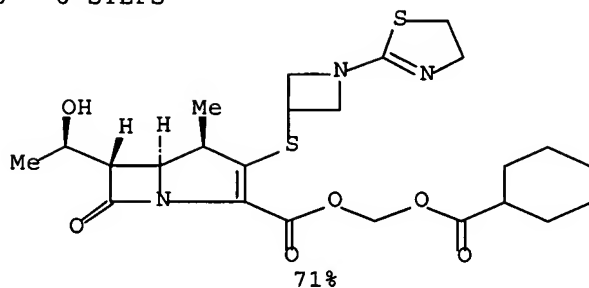


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(82) OF 126 - 6 STEPS

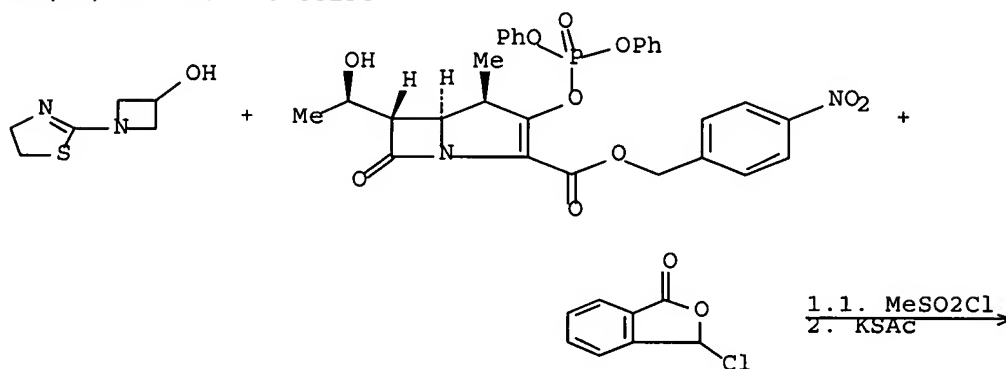


RX(82) OF 126 - 6 STEPS

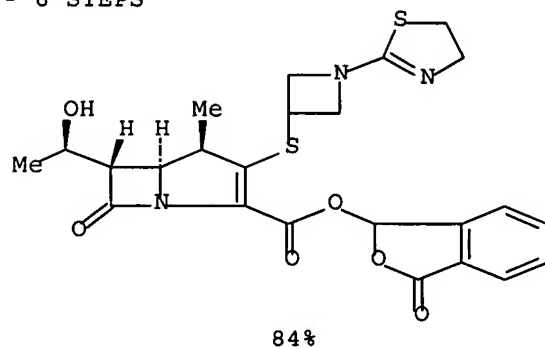


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(84) OF 126 - 6 STEPS

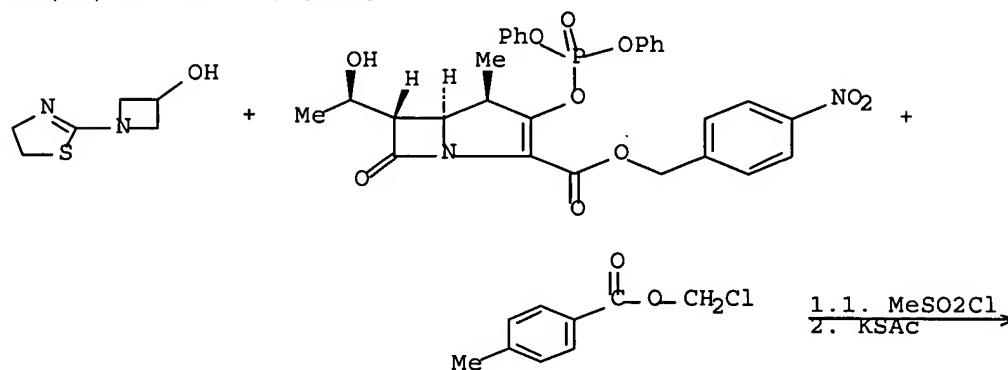


RX(84) OF 126 - 6 STEPS

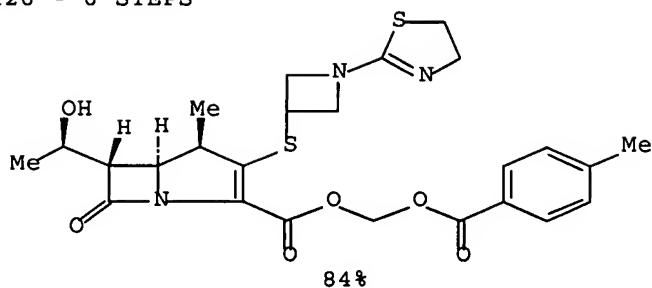


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(85) OF 126 - 6 STEPS

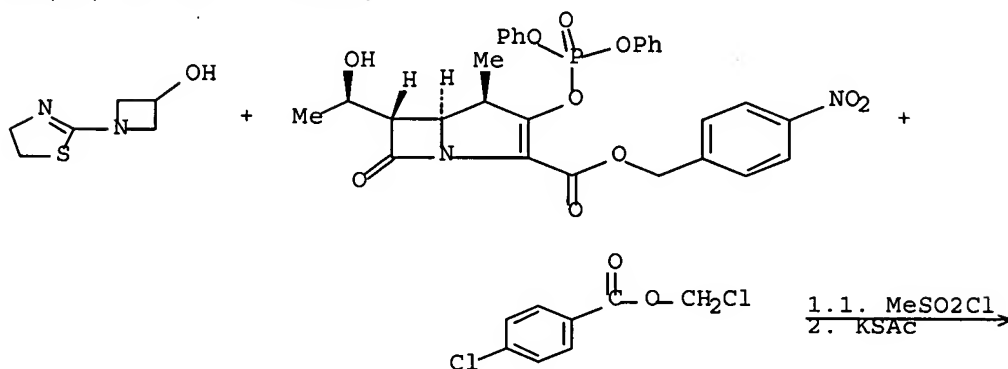


RX(85) OF 126 - 6 STEPS

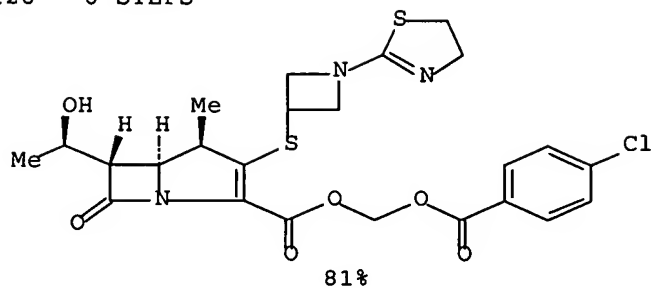


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(86) OF 126 - 6 STEPS

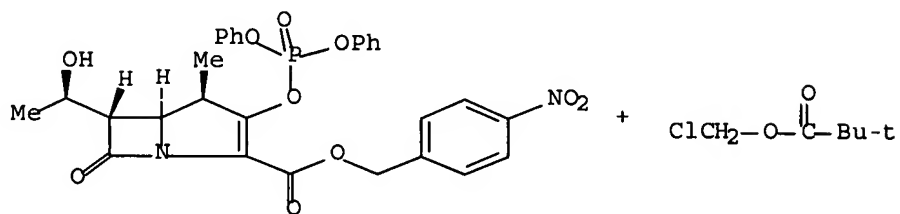
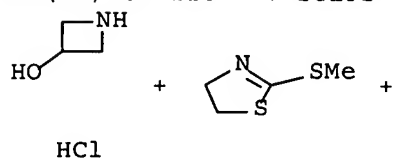


RX(86) OF 126 - 6 STEPS

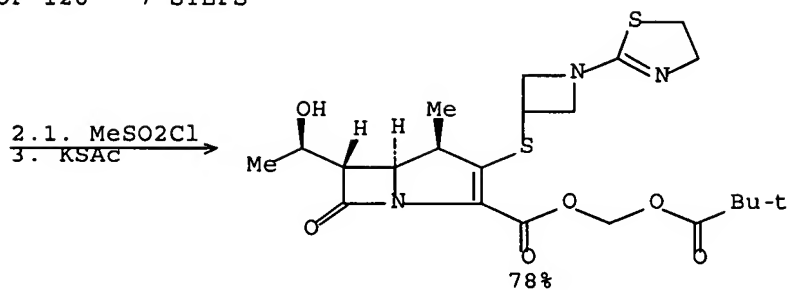


CON: STEP(1.1) 0.5 hours, 5 deg C  
 STEP(1.2) 10 minutes, room temperature  
 STEP(2) 5.5 hours, 100 deg C  
 STEP(3.1) 10 minutes, 5 deg C  
 STEP(3.2) 15 minutes  
 STEP(4.1) 2 hours, -20 deg C  
 STEP(4.2) 0.5 hours, 5 deg C  
 STEP(5.1) 1.5 hours, room temperature, 400 kPa  
 STEP(5.2) pH 5.6  
 STEP(6.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(6.2) 5 deg C, pH 4  
 STEP(6.3) pH 7.6

RX(87) OF 126 - 7 STEPS

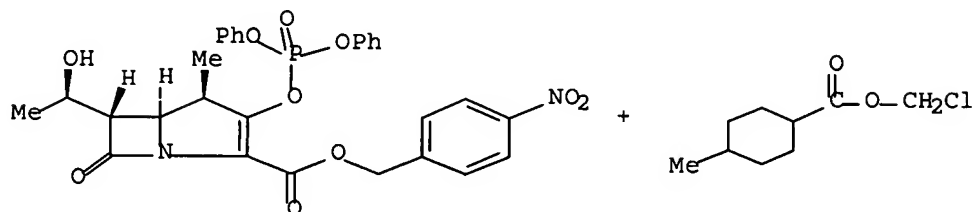
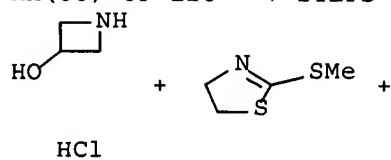


RX(87) OF 126 - 7 STEPS

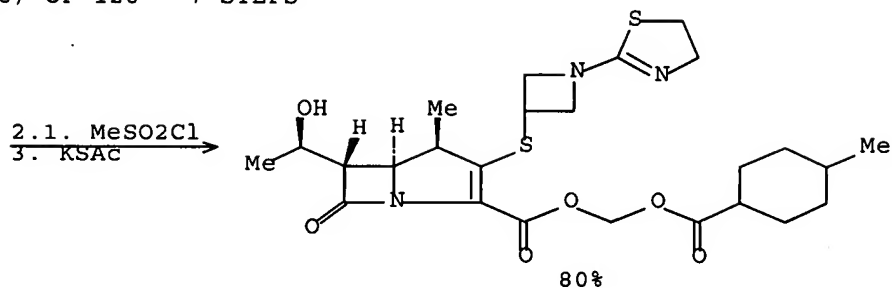


CON: STEP(1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(88) OF 126 - 7 STEPS

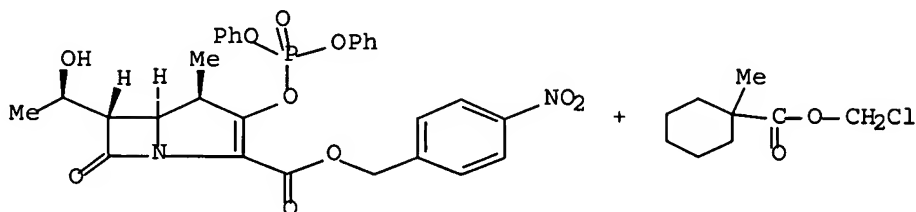
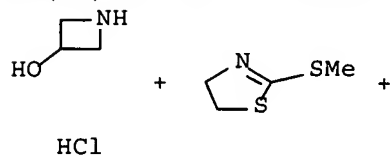


RX(88) OF 126 - 7 STEPS

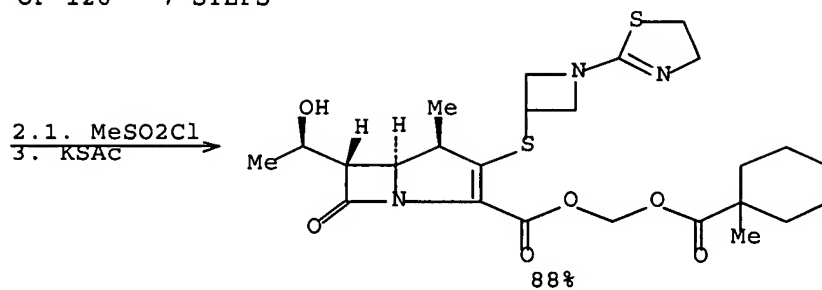


CON: STEP(1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(90) OF 126 - 7 STEPS

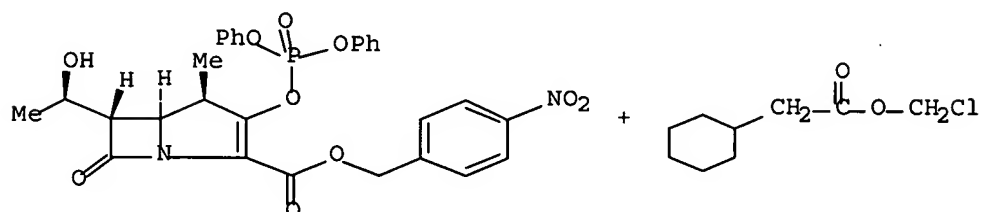
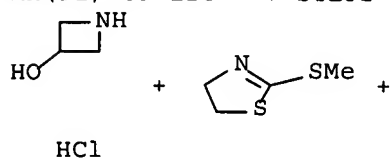


## RX(90) OF 126 - 7 STEPS

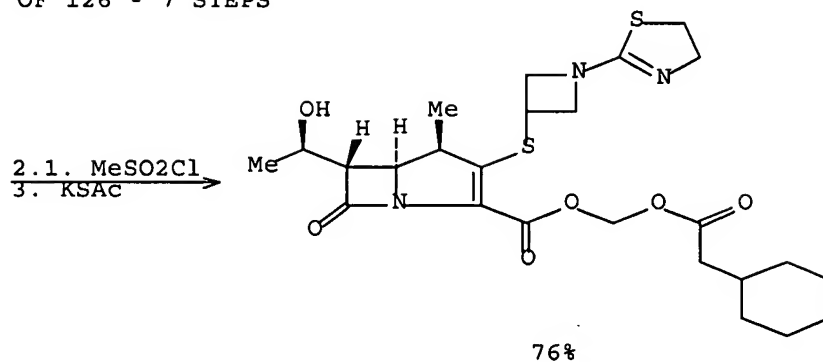


CON: STEP(1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

## RX(91) OF 126 - 7 STEPS

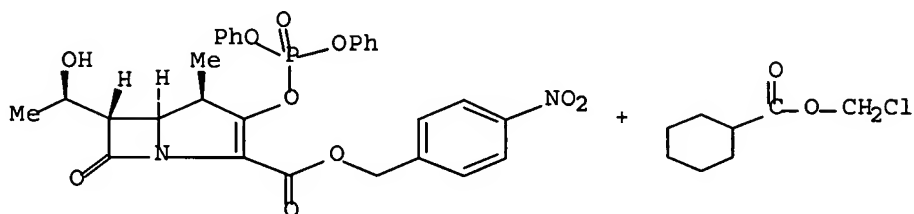
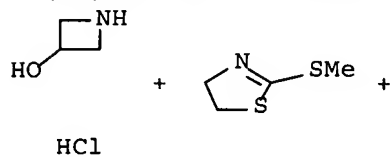


RX(91) OF 126 - 7 STEPS

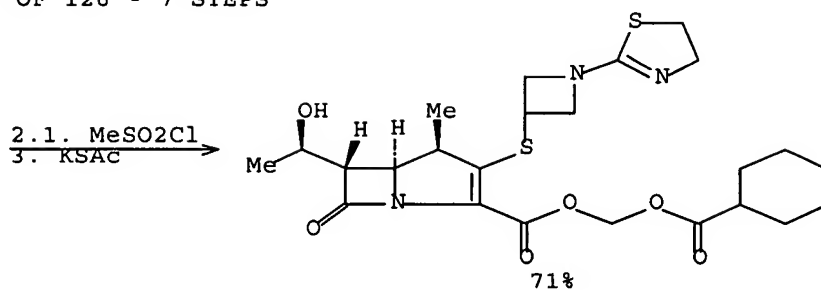


CON: STEP(1.1) 23 hours, reflux; reflux  $\rightarrow$  40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C  $\rightarrow$  5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(92) OF 126 - 7 STEPS

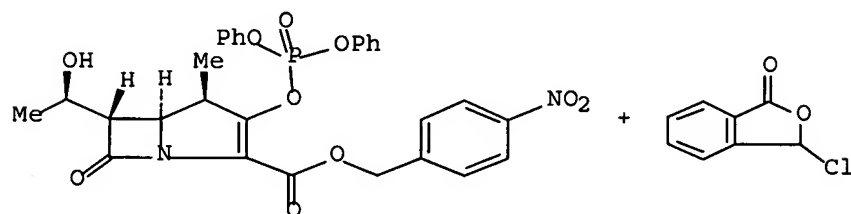
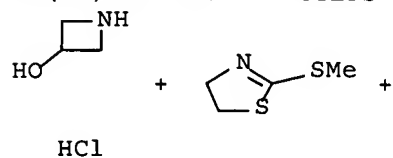


RX(92) OF 126 - 7 STEPS

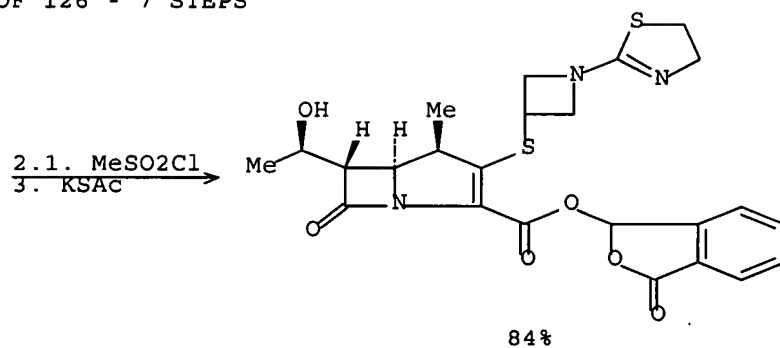


CON: STEP(1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(94) OF 126 - 7 STEPS

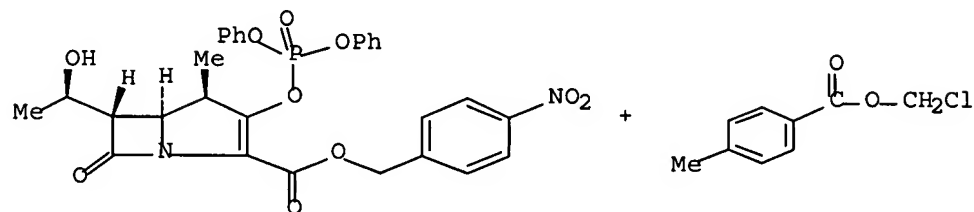
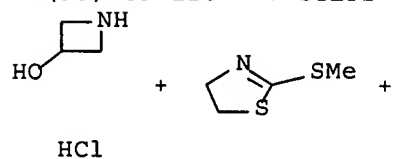


RX(94) OF 126 - 7 STEPS

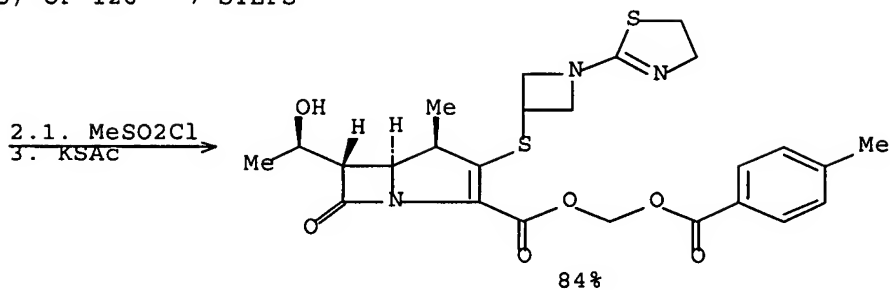


CON: STEP(1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(95) OF 126 - 7 STEPS

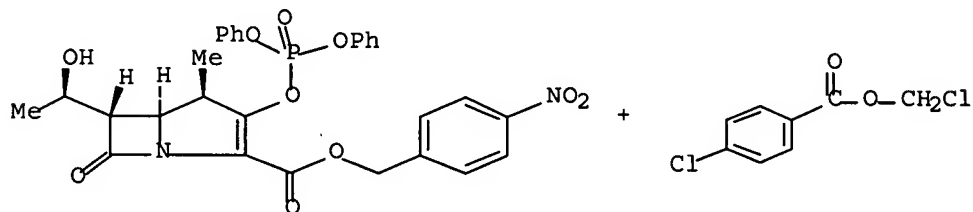
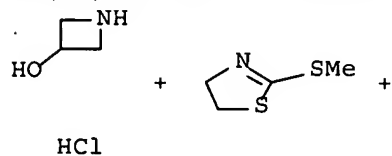


RX(95) OF 126 - 7 STEPS

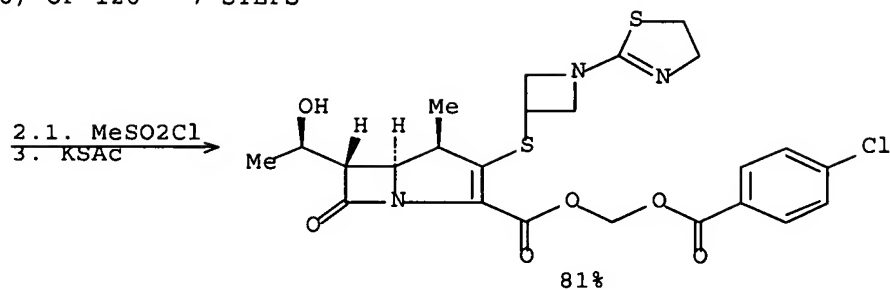


CON: STEP(1.1) 23 hours, reflux; reflux  $\rightarrow$  40 deg C  
 STEP(1.2) 2 hours, 40 deg C  
 STEP(2.1) 0.5 hours, 5 deg C  
 STEP(2.2) 10 minutes, room temperature  
 STEP(3) 5.5 hours, 100 deg C  
 STEP(4.1) 10 minutes, 5 deg C  
 STEP(4.2) 15 minutes  
 STEP(5.1) 2 hours, -20 deg C  
 STEP(5.2) 0.5 hours, 5 deg C  
 STEP(6.1) 1.5 hours, room temperature, 400 kPa  
 STEP(6.2) pH 5.6  
 STEP(7.1) 4 hours, 45 deg C; 45 deg C  $\rightarrow$  5 deg C  
 STEP(7.2) 5 deg C, pH 4  
 STEP(7.3) pH 7.6

RX(96) OF 126 - 7 STEPS

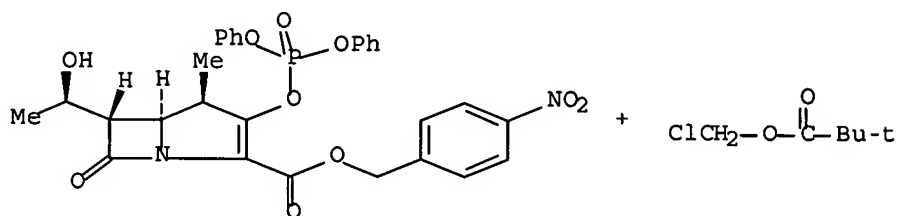
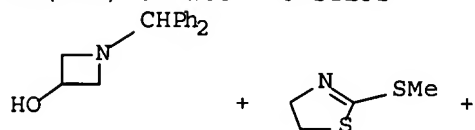


RX(96) OF 126 - 7 STEPS

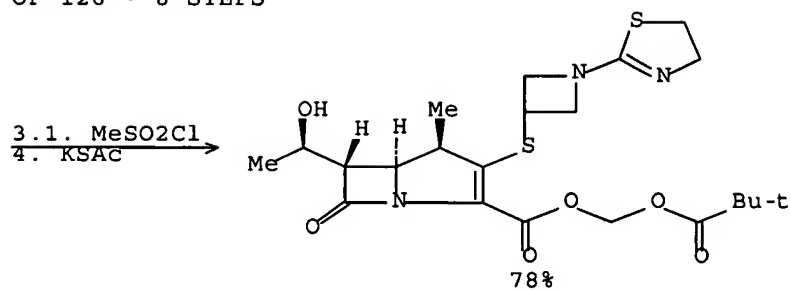


CON: STEP (1.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP (1.2) 2 hours, 40 deg C  
 STEP (2.1) 0.5 hours, 5 deg C  
 STEP (2.2) 10 minutes, room temperature  
 STEP (3) 5.5 hours, 100 deg C  
 STEP (4.1) 10 minutes, 5 deg C  
 STEP (4.2) 15 minutes  
 STEP (5.1) 2 hours, -20 deg C  
 STEP (5.2) 0.5 hours, 5 deg C  
 STEP (6.1) 1.5 hours, room temperature, 400 kPa  
 STEP (6.2) pH 5.6  
 STEP (7.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP (7.2) 5 deg C, pH 4  
 STEP (7.3) pH 7.6

RX(107) OF 126 - 8 STEPS

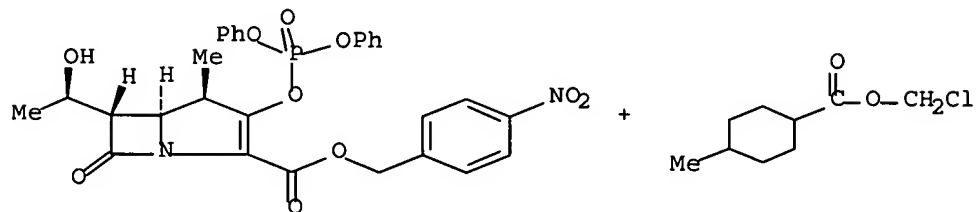
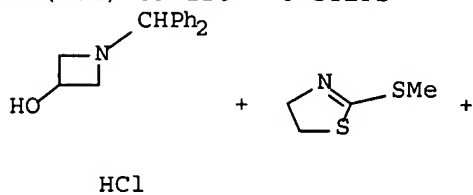


## RX(107) OF 126 - 8 STEPS

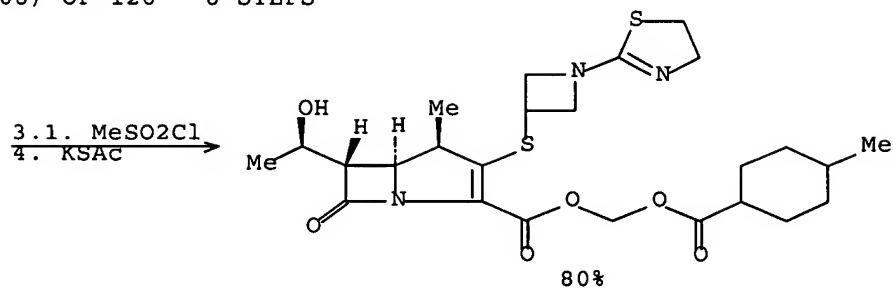


CON: STEP(1.1) 4 hours, room temperature, 350 kPa  
 STEP(2.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(2.2) 2 hours, 40 deg C  
 STEP(3.1) 0.5 hours, 5 deg C  
 STEP(3.2) 10 minutes, room temperature  
 STEP(4) 5.5 hours, 100 deg C  
 STEP(5.1) 10 minutes, 5 deg C  
 STEP(5.2) 15 minutes  
 STEP(6.1) 2 hours, -20 deg C  
 STEP(6.2) 0.5 hours, 5 deg C  
 STEP(7.1) 1.5 hours, room temperature, 400 kPa  
 STEP(7.2) pH 5.6  
 STEP(8.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(8.2) 5 deg C, pH 4  
 STEP(8.3) pH 7.6

## RX(108) OF 126 - 8 STEPS

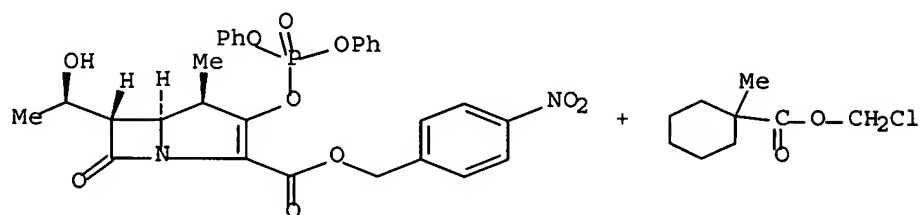
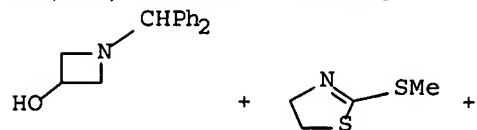


RX(108) OF 126 - 8 STEPS

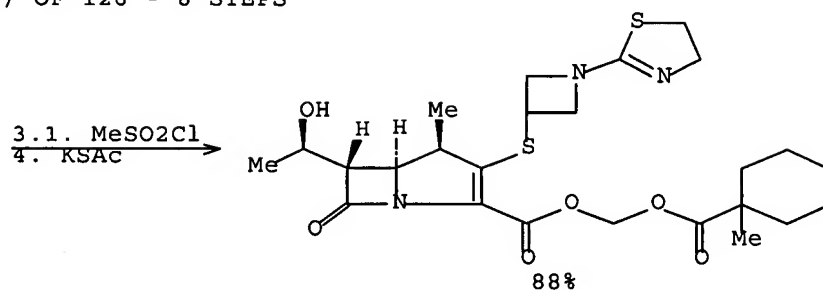


CON: STEP(1.1) 4 hours, room temperature, 350 kPa  
 STEP(2.1) 23 hours, reflux; reflux  $\rightarrow$  40 deg C  
 STEP(2.2) 2 hours, 40 deg C  
 STEP(3.1) 0.5 hours, 5 deg C  
 STEP(3.2) 10 minutes, room temperature  
 STEP(4) 5.5 hours, 100 deg C  
 STEP(5.1) 10 minutes, 5 deg C  
 STEP(5.2) 15 minutes  
 STEP(6.1) 2 hours, -20 deg C  
 STEP(6.2) 0.5 hours, 5 deg C  
 STEP(7.1) 1.5 hours, room temperature, 400 kPa  
 STEP(7.2) pH 5.6  
 STEP(8.1) 4 hours, 45 deg C; 45 deg C  $\rightarrow$  5 deg C  
 STEP(8.2) 5 deg C, pH 4  
 STEP(8.3) pH 7.6

RX(110) OF 126 - 8 STEPS

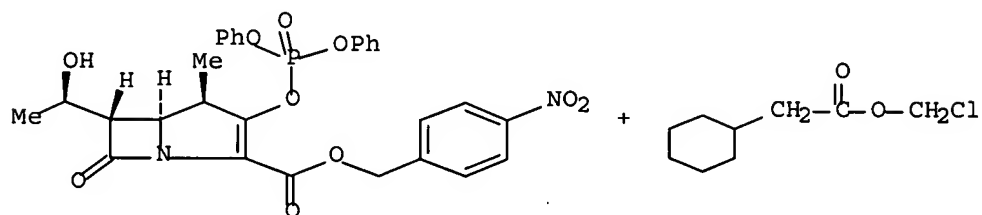
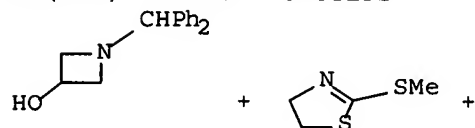


RX(110) OF 126 - 8 STEPS

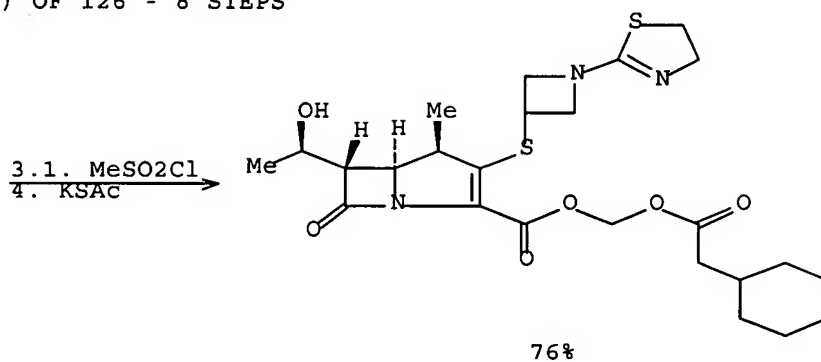


CON: STEP(1.1) 4 hours, room temperature, 350 kPa  
 STEP(2.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(2.2) 2 hours, 40 deg C  
 STEP(3.1) 0.5 hours, 5 deg C  
 STEP(3.2) 10 minutes, room temperature  
 STEP(4) 5.5 hours, 100 deg C  
 STEP(5.1) 10 minutes, 5 deg C  
 STEP(5.2) 15 minutes  
 STEP(6.1) 2 hours, -20 deg C  
 STEP(6.2) 0.5 hours, 5 deg C  
 STEP(7.1) 1.5 hours, room temperature, 400 kPa  
 STEP(7.2) pH 5.6  
 STEP(8.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(8.2) 5 deg C, pH 4  
 STEP(8.3) pH 7.6

RX(111) OF 126 - 8 STEPS

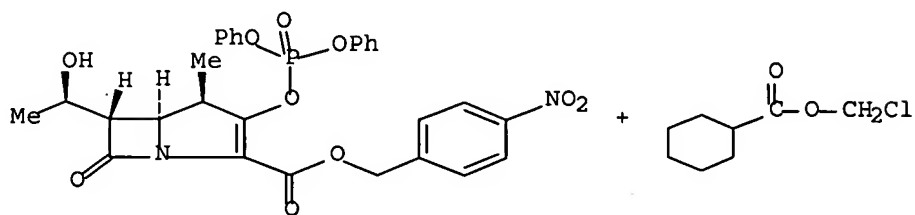
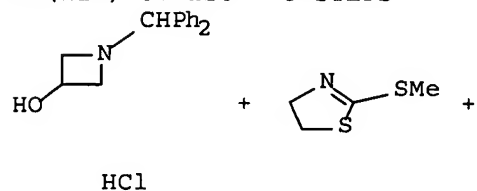


RX(111) OF 126 - 8 STEPS

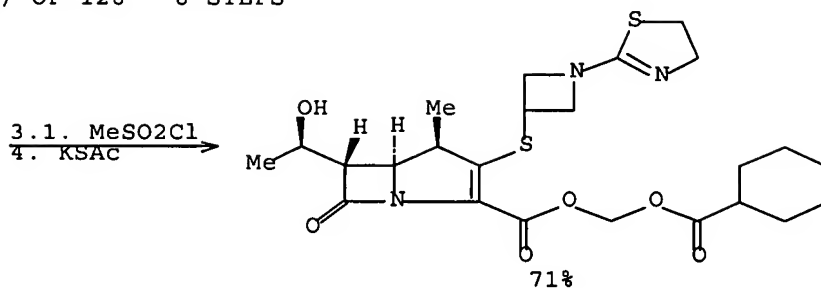


CON: STEP (1.1) 4 hours, room temperature, 350 kPa  
 STEP (2.1) 23 hours, reflux, reflux  $\rightarrow$  40 deg C  
 STEP (2.2) 2 hours, 40 deg C  
 STEP (3.1) 0.5 hours, 5 deg C  
 STEP (3.2) 10 minutes, room temperature  
 STEP (4) 5.5 hours, 100 deg C  
 STEP (5.1) 10 minutes, 5 deg C  
 STEP (5.2) 15 minutes  
 STEP (6.1) 2 hours, -20 deg C  
 STEP (6.2) 0.5 hours, 5 deg C  
 STEP (7.1) 1.5 hours, room temperature, 400 kPa  
 STEP (7.2) pH 5.6  
 STEP (8.1) 4 hours, 45 deg C; 45 deg C  $\rightarrow$  5 deg C  
 STEP (8.2) 5 deg C, pH 4  
 STEP (8.3) pH 7.6

RX(112) OF 126 - 8 STEPS

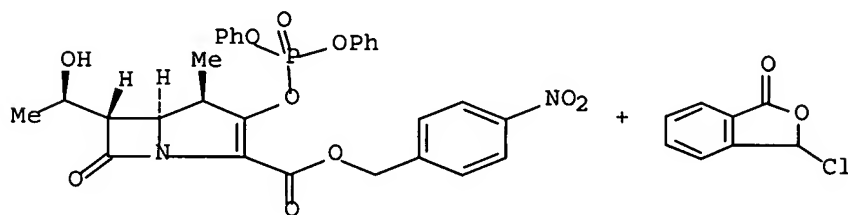
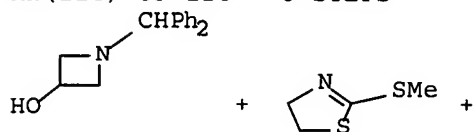


RX(112) OF 126 - 8 STEPS

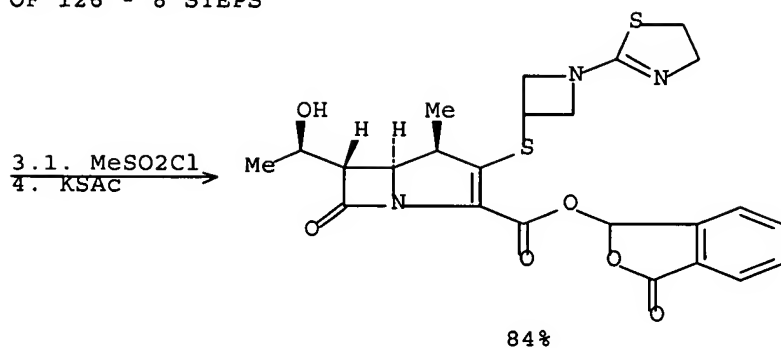


CON: STEP(1.1) 4 hours, room temperature, 350 kPa  
 STEP(2.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(2.2) 2 hours, 40 deg C  
 STEP(3.1) 0.5 hours, 5 deg C  
 STEP(3.2) 10 minutes, room temperature  
 STEP(4.1) 5.5 hours, 100 deg C  
 STEP(5.1) 10 minutes, 5 deg C  
 STEP(5.2) 15 minutes  
 STEP(6.1) 2 hours, -20 deg C  
 STEP(6.2) 0.5 hours, 5 deg C  
 STEP(7.1) 1.5 hours, room temperature, 400 kPa  
 STEP(7.2) pH 5.6  
 STEP(8.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(8.2) 5 deg C, pH 4  
 STEP(8.3) pH 7.6

RX(114) OF 126 - 8 STEPS

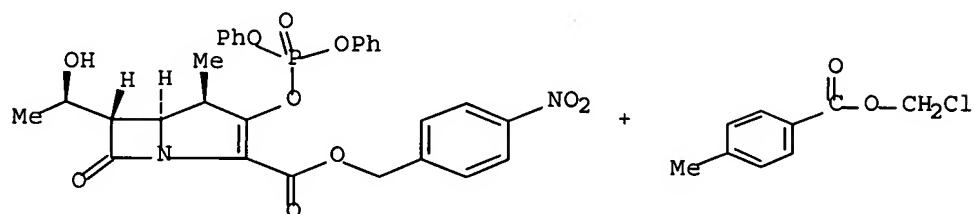
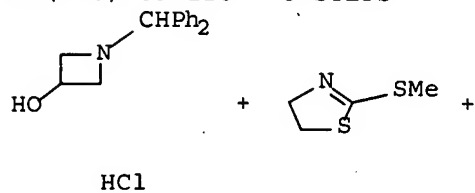


RX(114) OF 126 - 8 STEPS

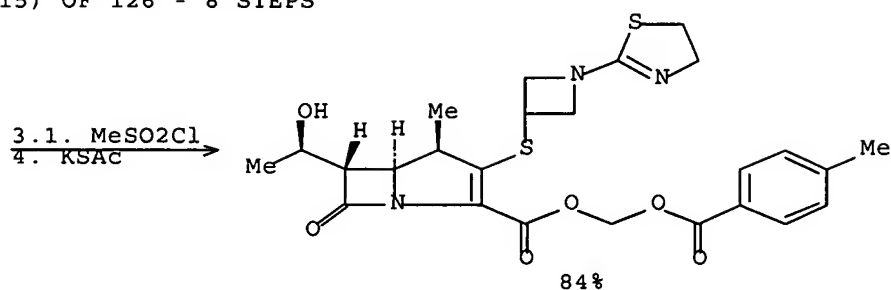


CON: STEP (1.1) 4 hours, room temperature, 350 kPa  
 STEP (2.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP (2.2) 2 hours, 40 deg C  
 STEP (3.1) 0.5 hours, 5 deg C  
 STEP (3.2) 10 minutes, room temperature  
 STEP (4) 5.5 hours, 100 deg C  
 STEP (5.1) 10 minutes, 5 deg C  
 STEP (5.2) 15 minutes  
 STEP (6.1) 2 hours, -20 deg C  
 STEP (6.2) 0.5 hours, 5 deg C  
 STEP (7.1) 1.5 hours, room temperature, 400 kPa  
 STEP (7.2) pH 5.6  
 STEP (8.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP (8.2) 5 deg C, pH 4  
 STEP (8.3) pH 7.6

RX(115) OF 126 - 8 STEPS

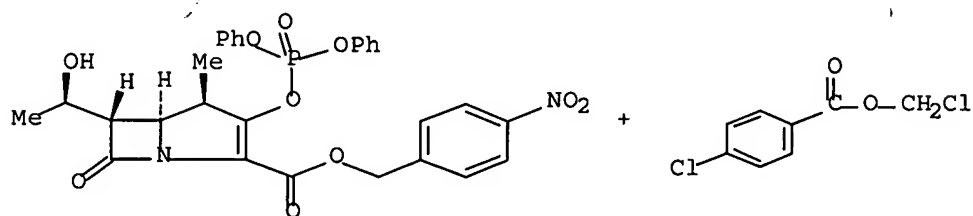
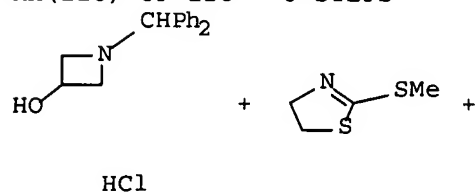


RX(115) OF 126 - 8 STEPS

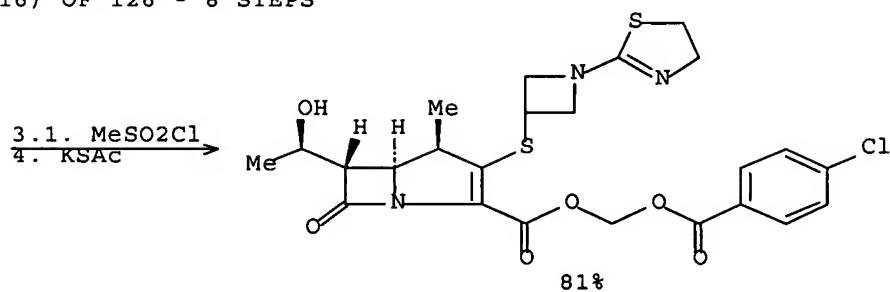


CON: STEP(1.1) 4 hours, room temperature, 350 kPa  
 STEP(2.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(2.2) 2 hours, 40 deg C  
 STEP(3.1) 0.5 hours, 5 deg C  
 STEP(3.2) 10 minutes, room temperature  
 STEP(4) 5.5 hours, 100 deg C  
 STEP(5.1) 10 minutes, 5 deg C  
 STEP(5.2) 15 minutes  
 STEP(6.1) 2 hours, -20 deg C  
 STEP(6.2) 0.5 hours, 5 deg C  
 STEP(7.1) 1.5 hours, room temperature, 400 kPa  
 STEP(7.2) pH 5.6  
 STEP(8.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(8.2) 5 deg C, pH 4  
 STEP(8.3) pH 7.6

RX(116) OF 126 - 8 STEPS

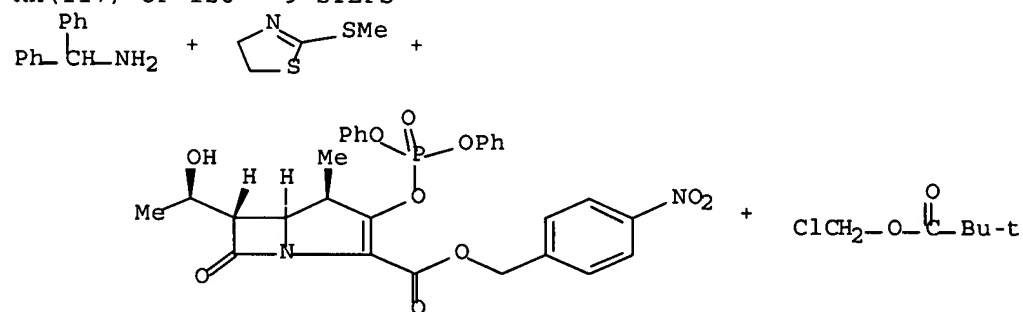


RX(116) OF 126 - 8 STEPS



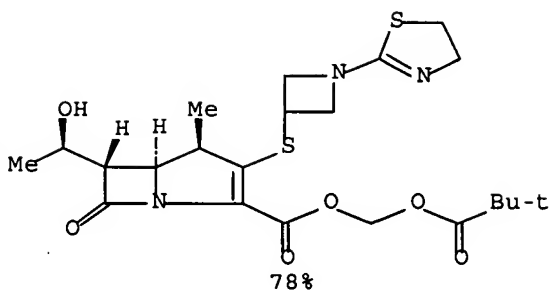
CON: STEP (1.1) 4 hours, room temperature, 350 kPa  
 STEP (2.1) 23 hours, reflux; reflux  $\rightarrow$  40 deg C  
 STEP (2.2) 2 hours, 40 deg C  
 STEP (3.1) 0.5 hours, 5 deg C  
 STEP (3.2) 10 minutes, room temperature  
 STEP (4) 5 hours, 100 deg C  
 STEP (5.1) 10 minutes, 5 deg C  
 STEP (5.2) 15 minutes  
 STEP (6.1) 2 hours, -20 deg C  
 STEP (6.2) 0.5 hours, 5 deg C  
 STEP (7.1) 1.5 hours, room temperature, 400 kPa  
 STEP (7.2) pH 5.6  
 STEP (8.1) 4 hours, 45 deg C; 45 deg C  $\rightarrow$  5 deg C  
 STEP (8.2) 5 deg C, pH 4  
 STEP (8.3) pH 7.6

RX(117) OF 126 - 9 STEPS



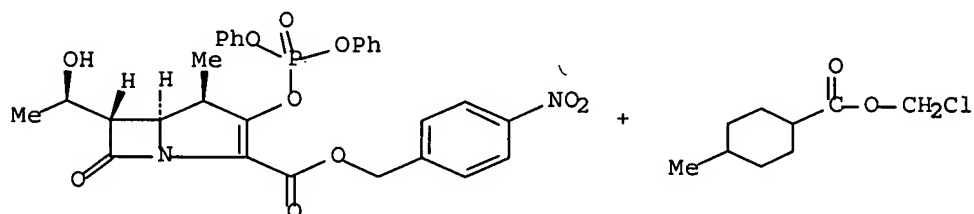
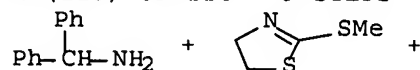
## RX(117) OF 126 - 9 STEPS

1.1. Epichlorohydrin  
4.1. MeSO<sub>2</sub>Cl  
5. KSAC



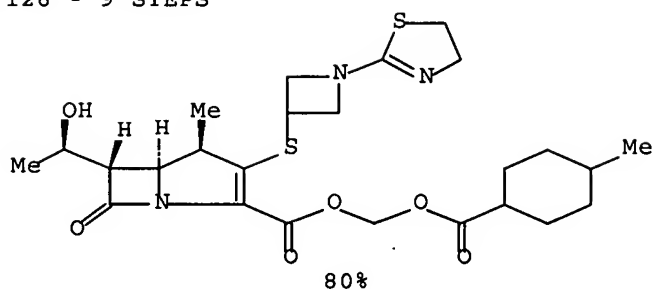
CON: STEP(1.1) 1 day, room temperature  
STEP(1.2) 3 days, 50 deg C  
STEP(2.1) 4 hours, room temperature, 350 kPa  
STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
STEP(3.2) 2 hours, 40 deg C  
STEP(4.1) 0.5 hours, 5 deg C  
STEP(4.2) 10 minutes, room temperature  
STEP(5) 5.5 hours, 100 deg C  
STEP(6.1) 10 minutes, 5 deg C  
STEP(6.2) 15 minutes  
STEP(7.1) 2 hours, -20 deg C  
STEP(7.2) 0.5 hours, 5 deg C  
STEP(8.1) 1.5 hours, room temperature, 400 kPa  
STEP(8.2) pH 5.6  
STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
STEP(9.2) 5 deg C, pH 4  
STEP(9.3) pH 7.6

## RX(118) OF 126 - 9 STEPS



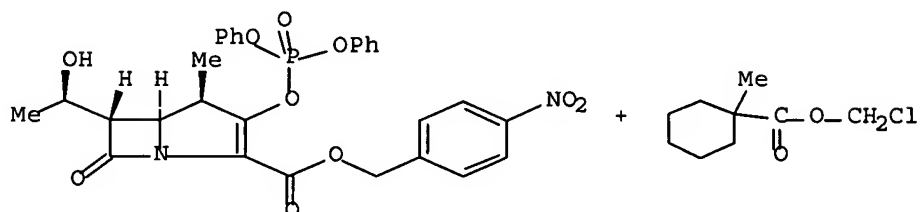
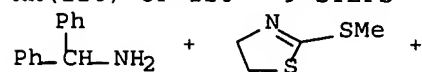
1.1. Epichlorohydrin  
4.1. MeSO<sub>2</sub>Cl  
5. KSAC

RX(118) OF 126 - 9 STEPS



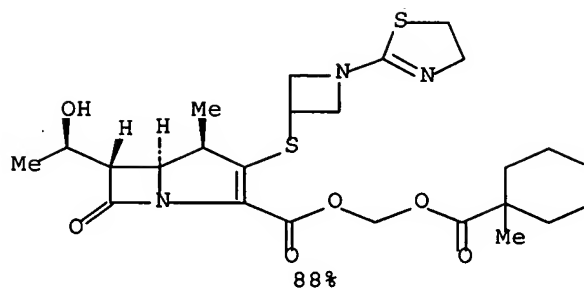
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

RX(120) OF 126 - 9 STEPS



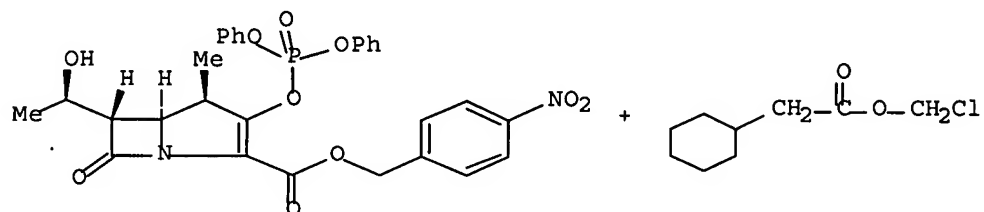
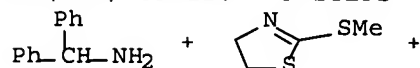
RX(120) OF 126 - 9 STEPS

1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC



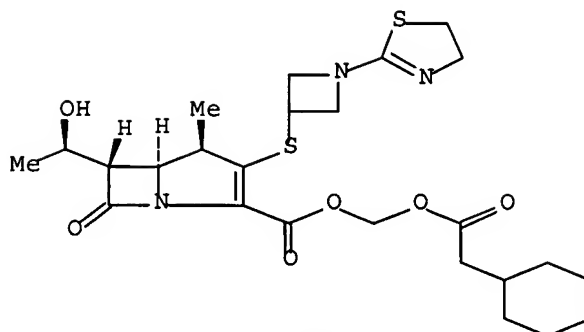
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

RX(121) OF 126 - 9 STEPS



## RX(121) OF 126 - 9 STEPS

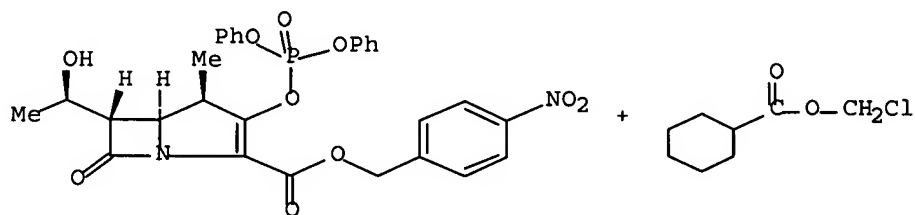
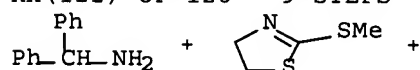
1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC



76%

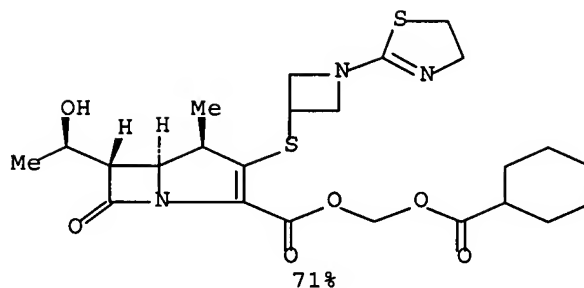
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5.5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

## RX(122) OF 126 - 9 STEPS



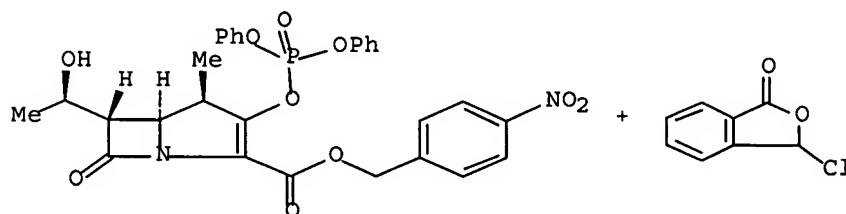
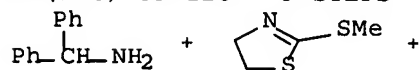
RX(122) OF 126 - 9 STEPS

1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC



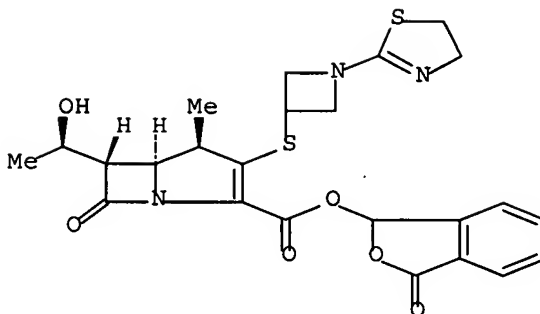
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

RX(124) OF 126 - 9 STEPS



RX(124) OF 126 - 9 STEPS

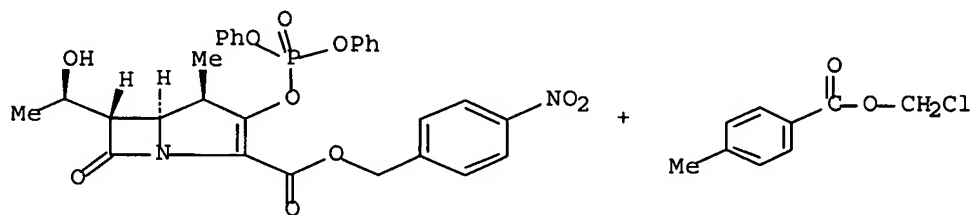
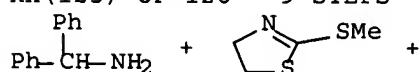
1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC



84%

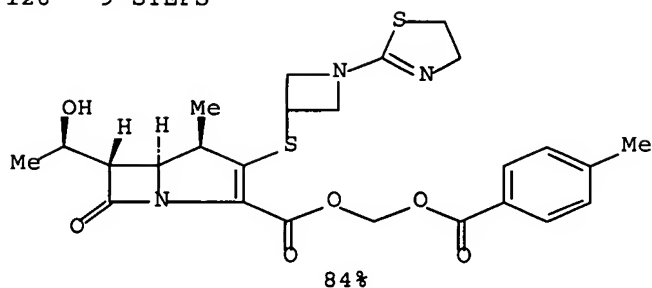
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

RX(125) OF 126 - 9 STEPS



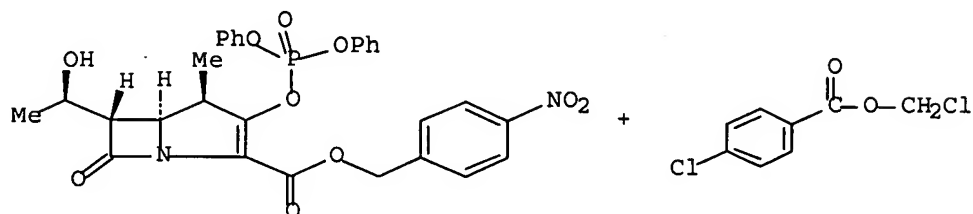
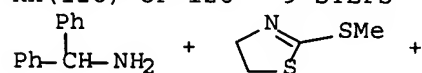
1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC

RX(125) OF 126 - 9 STEPS



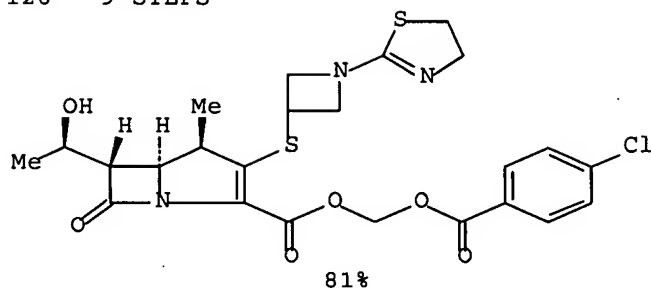
CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5.5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

RX(126) OF 126 - 9 STEPS



1.1. Epichlorohydrin  
 4.1. MeSO<sub>2</sub>Cl  
 5. KSAC

RX(126) OF 126 - 9 STEPS



CON: STEP(1.1) 1 day, room temperature  
 STEP(1.2) 3 days, 50 deg C  
 STEP(2.1) 4 hours, room temperature, 350 kPa  
 STEP(3.1) 23 hours, reflux; reflux -> 40 deg C  
 STEP(3.2) 2 hours, 40 deg C  
 STEP(4.1) 0.5 hours, 5 deg C  
 STEP(4.2) 10 minutes, room temperature  
 STEP(5) 5.5 hours, 100 deg C  
 STEP(6.1) 10 minutes, 5 deg C  
 STEP(6.2) 15 minutes  
 STEP(7.1) 2 hours, -20 deg C  
 STEP(7.2) 0.5 hours, 5 deg C  
 STEP(8.1) 1.5 hours, room temperature, 400 kPa  
 STEP(8.2) pH 5.6  
 STEP(9.1) 4 hours, 45 deg C; 45 deg C -> 5 deg C  
 STEP(9.2) 5 deg C, pH 4  
 STEP(9.3) pH 7.6

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 4 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 127:156255 CASREACT Full-text

TITLE: Synthesis and structure-activity relationships of a novel oral carbapenem, CS-834

AUTHOR(S): Miyauchi, Masao; Endo, Rokuro; Hisaoka, Masafumi; Yasuda, Hiroshi; Kawamoto, Isao

CORPORATE SOURCE: Research Laboratories, Sankyo Co., Ltd., Shinagawaku, 140, Japan

SOURCE: Journal of Antibiotics (1997), 50(5), 429-439  
 CODEN: JANTAJ; ISSN: 0021-8820

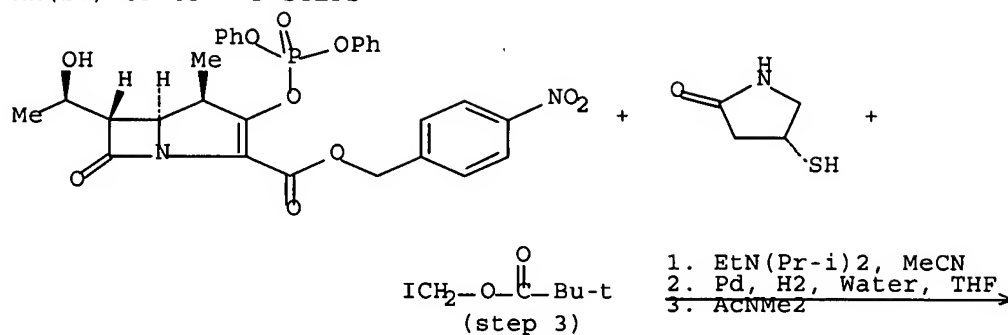
PUBLISHER: Japan Antibiotics Research Association

DOCUMENT TYPE: Journal

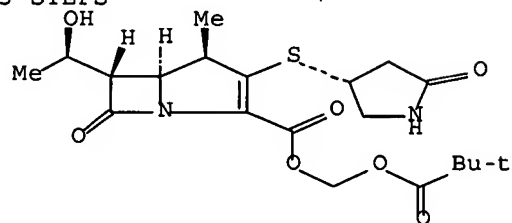
LANGUAGE: English

AB The authors have studied an ester prodrug of a carbapenem to develop a potent orally active  $\beta$ -lactam antibiotic. A variety of 1 $\beta$ -methylcarbapenem derivs. have been synthesized. The authors have found that some derivs. having an amide group in the C-2 side chain show potent and well balanced antibacterial activities as well as high stability against dehydropeptidase-I. Oral absorption of derivs. has been optimized by modifying the C-3 ester promoity. Pivaloyloxymethyl (1R,5S,6S)-6[(R)-1-hydroxyethyl]-1-methyl-2-[(R)-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate, CS-834, has been selected as the most promising compound for further evaluation.

RX(27) OF 63 - 3 STEPS



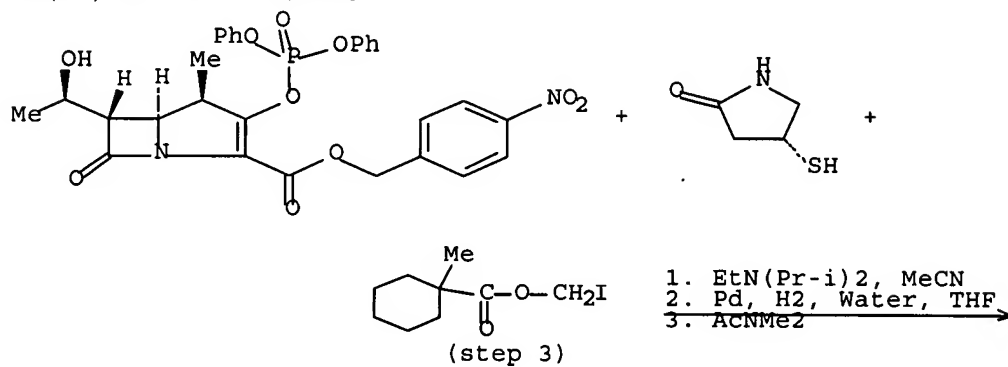
RX(27) OF 63 - 3 STEPS



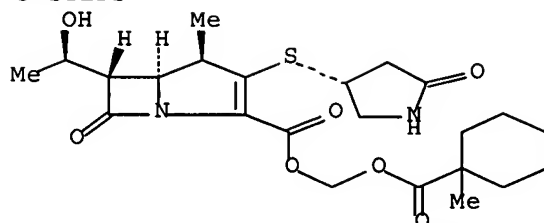
61%

NOTE: 2) PHOSPHATE BUFFER, S-ANALOG SIMILARLY PREPD.

RX(28) OF 63 - 3 STEPS

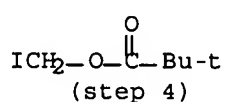
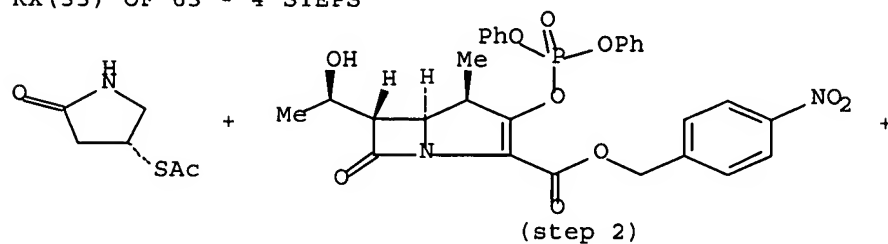


RX(28) OF 63 - 3 STEPS



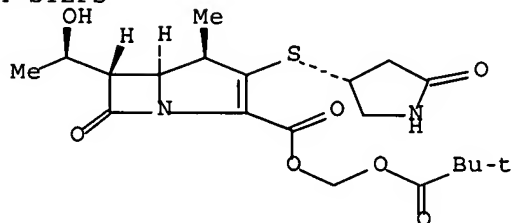
NOTE: 2) PHOSPHATE BUFFER, S-ANALOG SIMILARLY PREPD.

RX(33) OF 63 - 4 STEPS



1.1. NaOMe, MeOH  
 1.2. HCl, Water  
 2. EtN(Pr-i)<sub>2</sub>, MeCN  
 3. Pd, H<sub>2</sub>, Water, THF  
 4. AcNMe<sub>2</sub>

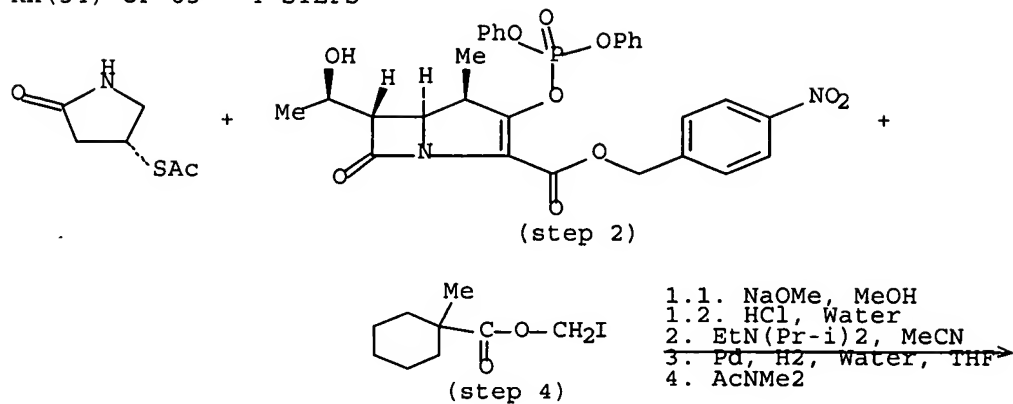
RX(33) OF 63 - 4 STEPS



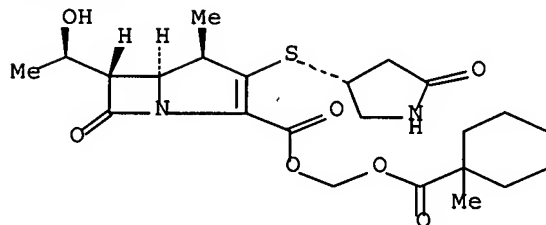
61%

NOTE: 1) S-ANALOG SIMILARLY PREPD., 3) PHOSPHATE BUFFER, S-ANALOG SIMILARLY PREPD.

RX(34) OF 63 - 4 STEPS

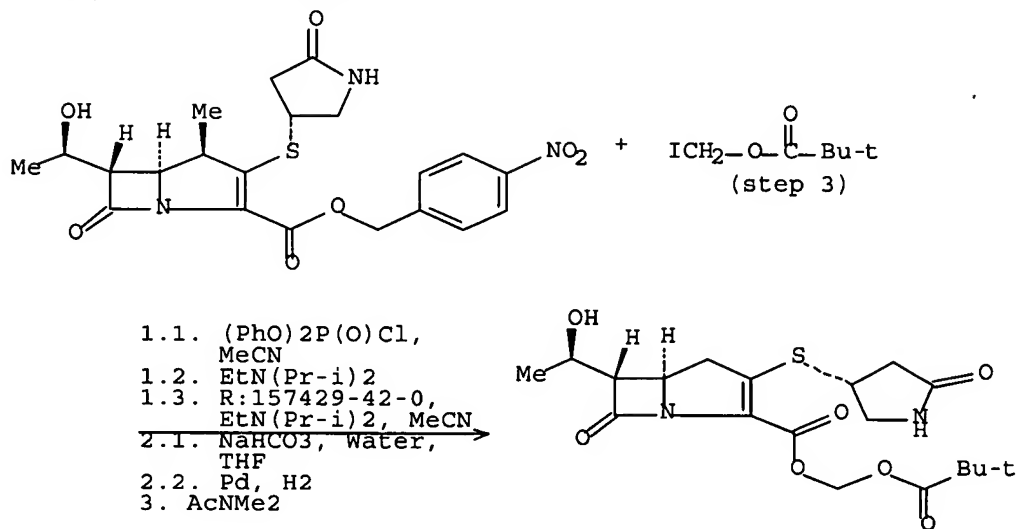


RX(34) OF 63 - 4 STEPS

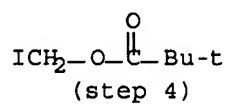
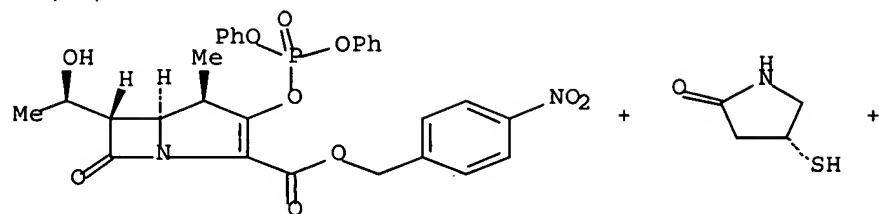


NOTE: 1) S-ANALOG SIMILARLY PREPD., 3) PHOSPHATE BUFFER, S-ANALOG  
 SIMILARLY PREPD.

RX(45) OF 63 - 3 STEPS

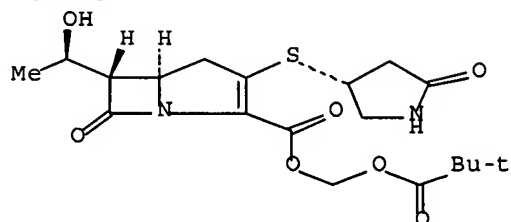


RX(46) OF 63 - 4 STEPS

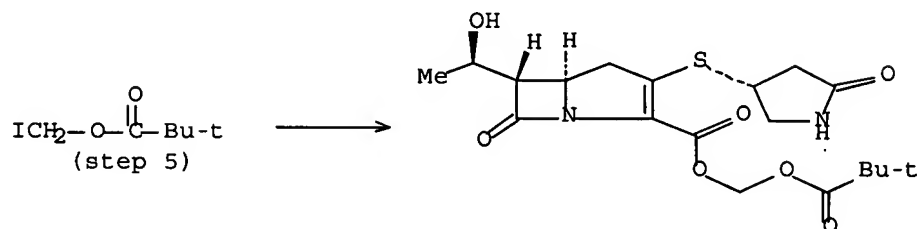
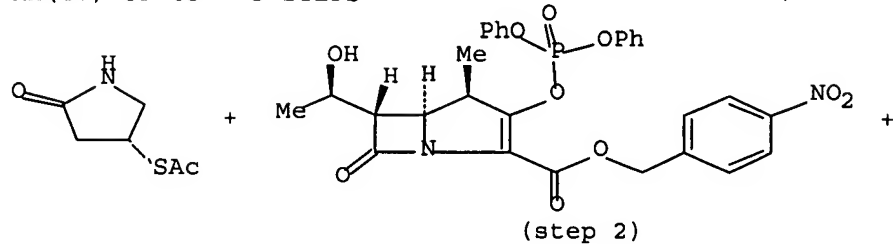


1. EtN(Pr-i)2, MeCN
- 2.1. (PhO)2P(O)Cl, MeCN
- 2.2. EtN(Pr-i)2
- 2.3. R:157429-42-0, EtN(Pr-i)2, MeCN
- 3.1. NaHCO3, Water, THF
- 3.2. Pd, H2
4. AcNMe2

RX(46) OF 63 - 4 STEPS

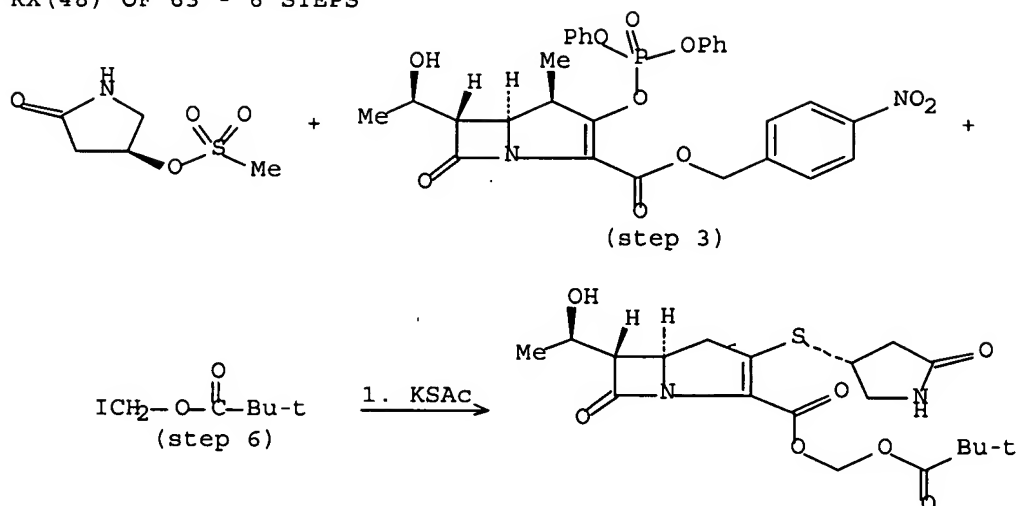


RX(47) OF 63 - 5 STEPS



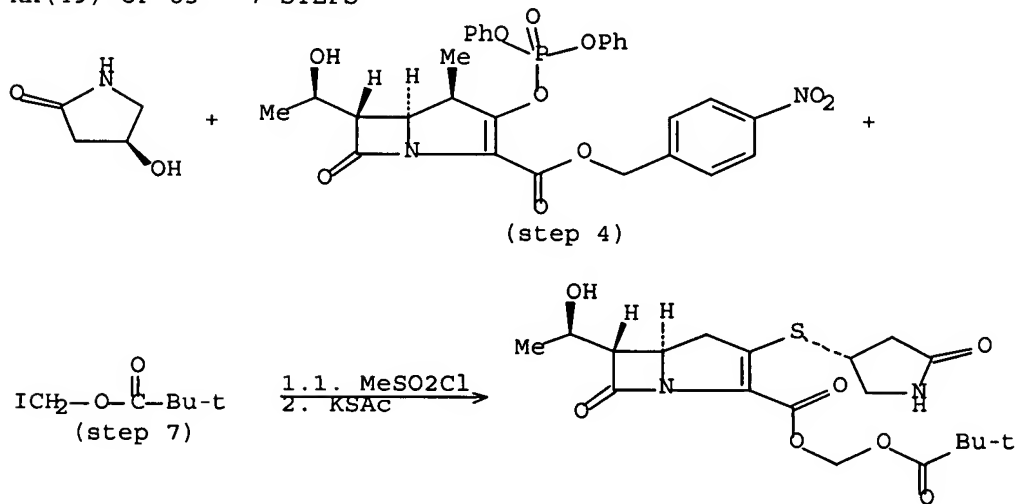
NOTE: 1) S-ANALOG SIMILARLY PREPD.

RX(48) OF 63 - 6 STEPS



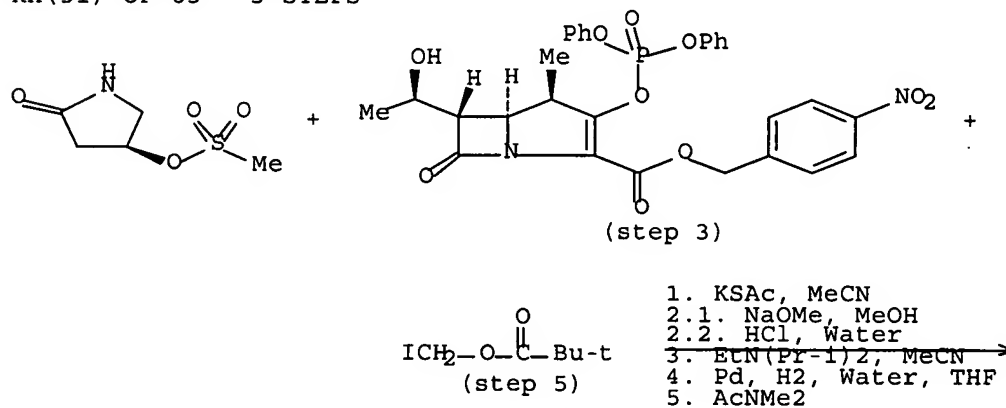
NOTE: 2) S-ANALOG SIMILARLY PREPD.

RX(49) OF 63 - 7 STEPS

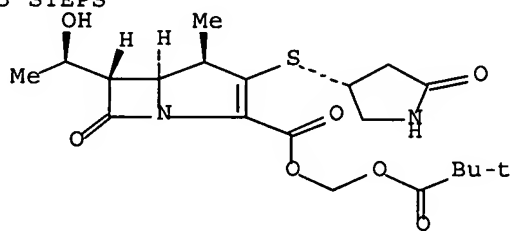


NOTE: 3) S-ANALOG SIMILARLY PREPD.

RX(51) OF 63 - 5 STEPS

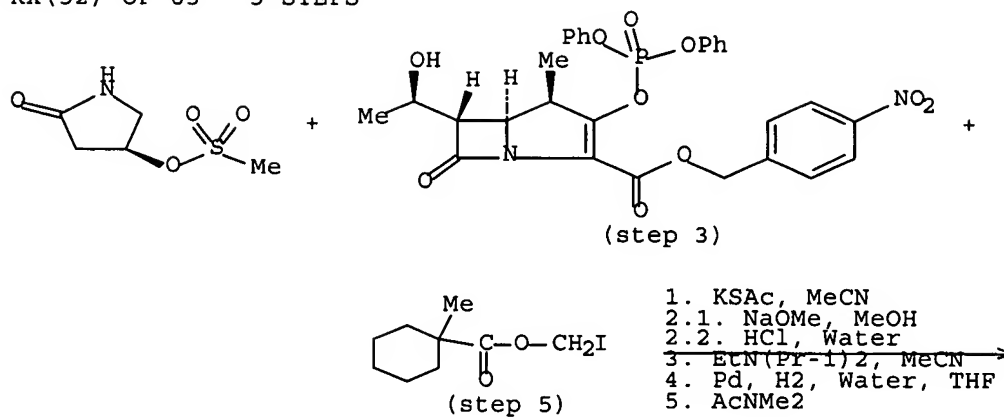


RX(51) OF 63 - 5 STEPS

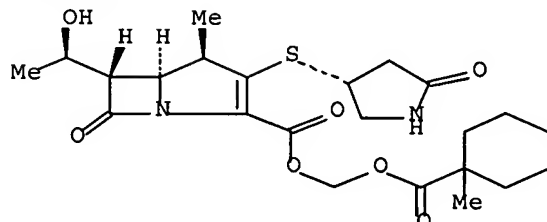


NOTE: 2) S-ANALOG SIMILARLY PREPD., 4) PHOSPHATE BUFFER, S-ANALOG SIMILARLY PREPD.

RX(52) OF 63 - 5 STEPS

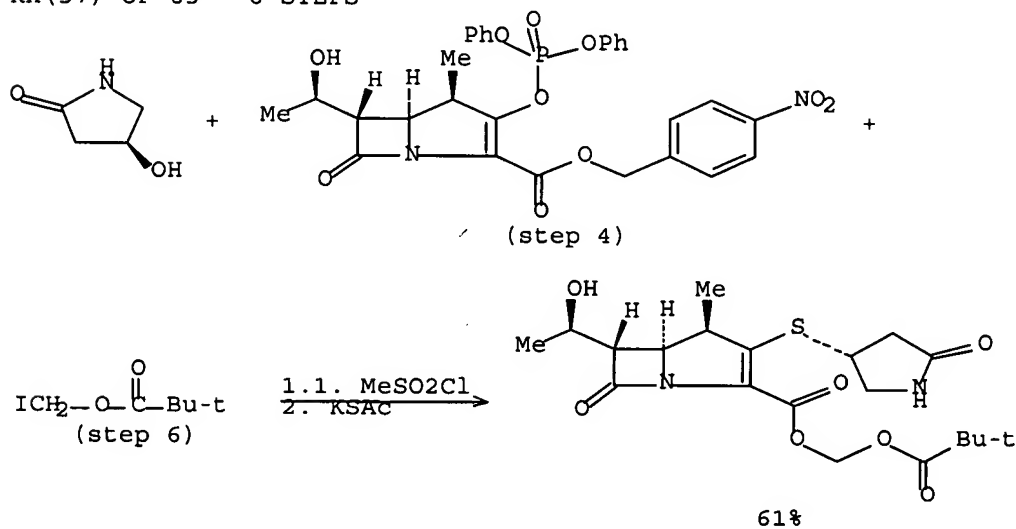


RX(52) OF 63 - 5 STEPS



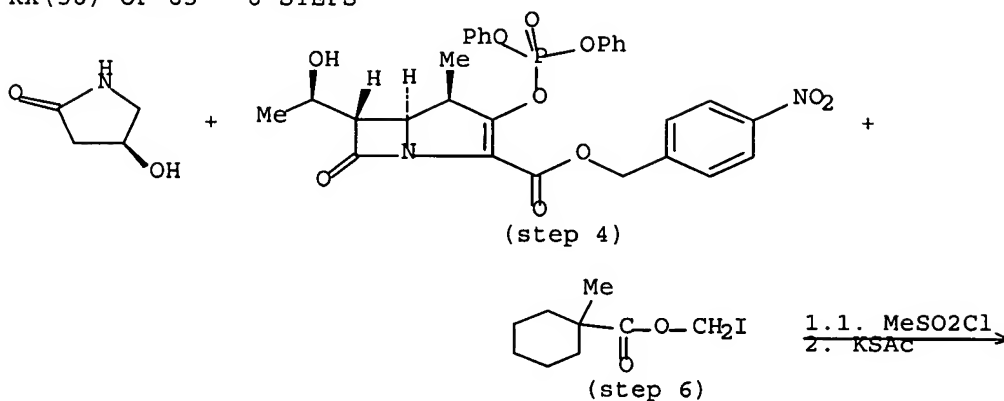
NOTE: 2) S-ANALOG SIMILARLY PREPD., 4) PHOSPHATE BUFFER, S-ANALOG SIMILARLY PREPD.

RX(57) OF 63 - 6 STEPS



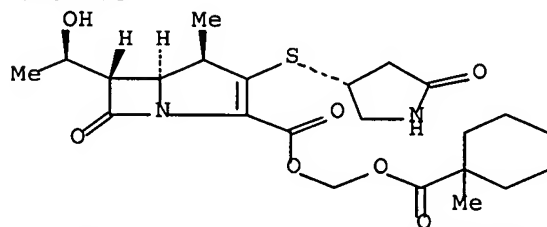
NOTE: 3) S-ANALOG SIMILARLY PREPD., 5) PHOSPHATE BUFFER, S-ANALOG  
SIMILARLY PREPD.

RX(58) OF 63 - 6 STEPS



1

RX(58) OF 63 - 6 STEPS



NOTE: 3) S-ANALOG SIMILARLY PREPD., 5) PHOSPHATE BUFFER, S-ANALOG  
SIMILARLY PREPD.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 4 CASREACT COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 125:328328 CASREACT Full-text  
TITLE: A New Synthesis of 1 $\beta$ -Alkylcarbapenems Utilizing  
Eschenmoser Sulfide Contraction of the Novel  
Thiazinone Intermediates  
AUTHOR(S): Sakurai, Osamu; Ogiku, Tsuyoshi; Takahashi, Masami;  
Hayashi, Masahito; Yamanaka, Takeshi; Horikawa,  
Hiroshi; Iwasaki, Tameo  
CORPORATE SOURCE: Lead Generation Research Laboratory, Tanabe Seiyaku  
Co. Ltd., Yodogawa, 532, Japan  
SOURCE: Journal of Organic Chemistry (1996), 61(22), 7889-7894

PUBLISHER:

CODEN: JOCEAH; ISSN: 0022-3263

DOCUMENT TYPE:

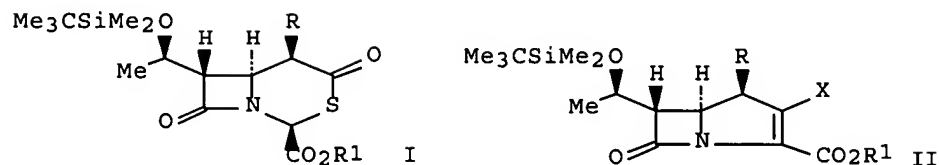
American Chemical Society

LANGUAGE:

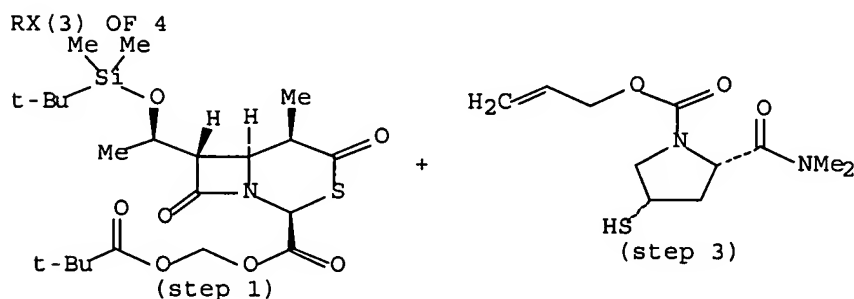
Journal

GI

English

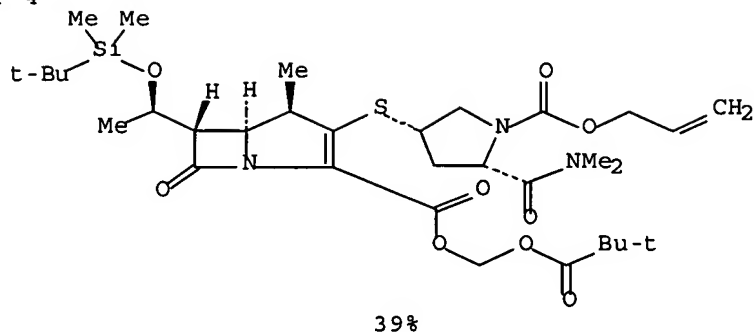


AB Novel syntheses of the 1 $\beta$ -alkylcarbapenems were achieved on the basis of Eschenmoser sulfide contraction of new bicyclic 1,3-thiazinone intermediates. 1,3-Thiazinones I [R = Me, CH<sub>2</sub>CH<sub>2</sub>OSiMe<sub>2</sub>CMe<sub>3</sub>; R<sub>1</sub> = allyl, CH<sub>2</sub>O<sub>2</sub>CCMe<sub>3</sub>] were effectively prepared from thioesters using a C(4)-S bond formation process. The sulfide contraction reactions were performed by treatment of I with base (NaH or KO<sup>t</sup>Bu) in the presence of triphenylphosphine to generate the carbapenem enolates which were trapped by (PhO)<sub>2</sub>P(O)Cl followed by reaction with mercaptans to afford carbapenems II [X = SCH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>CH:CH<sub>2</sub>, (3S,5S)-1-allyloxycarbonyl-2-N,N-dimethylcarbamoyl-5-pyrrolidinylthio].



1. PPh<sub>3</sub>, <sup>t</sup>-BuOK, PhMe  
 2. (PhO)<sub>2</sub>P(O)Cl, MeCN  
 3. EtN(Pr-1)<sub>2</sub>, DMF →

RX(3) OF 4



L8 ANSWER 4 OF 4 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 120:217089 CASREACT Full-text

TITLE: Process for preparing beta-lactam derivatives (carbapenems) and azathiabicycloalkanes as synthetic intermediates thereof

INVENTOR(S): Horikawa, Hiroshi; Kondo, Kazuhiko; Iwasaki, Tameo

PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

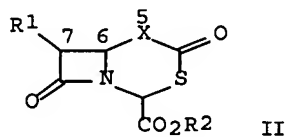
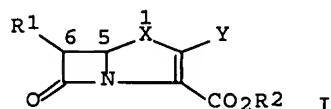
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 559533	A1	19930908	EP 1993-400506	19930226
EP 559533	B1	19980722		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 05279367	A	19931026	JP 1992-99023	19920306
JP 2569455	B2	19970108		
CA 2085540	A1	19930907	CA 1993-2085540	19930217
US 5414081	A	19950509	US 1993-18407	19930217
AT 168693	T	19980815	AT 1993-400506	19930226
ES 2119872	T3	19981016	ES 1993-400506	19930226
US 5589592	A	19961231	US 1995-393395	19950407
PRIORITY APPLN. INFO.:			JP 1992-99023	19920306
			US 1993-18407	19930217

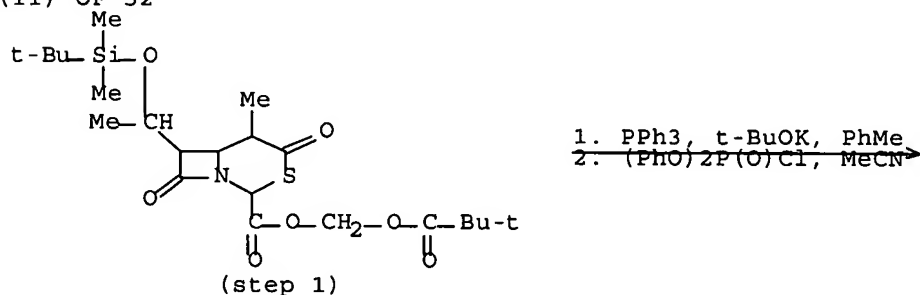
OTHER SOURCE(S): MARPAT 120:217089

GI

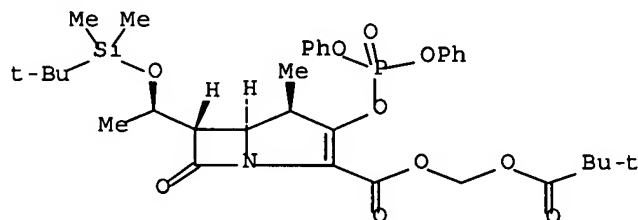


AB  $\beta$ -Lactams I [R1 = (un)protected hydroxyalkyl or amino; R2 = H, ester residue; X = CH<sub>2</sub>, alkylidene, S, ACH<sub>2</sub>; A = S, O, CH<sub>2</sub>; Y = OW, SR<sub>4</sub>; W = residue of active ester; R<sub>4</sub> = organic group] and salts are prepared by treating 1-aza-3-thiabicycloalkanes II with a base and a desulfurizing agent, followed by reaction with an active esterifying agent and possibly with a mercaptan R<sub>4</sub>SH. Thus, (3S,4S)-3-[(R)-1-tert-butyltrimethylsilyloxyethyl]-4-[(1R)-1-[2,2-bis(ethoxycarbonyl)ethylthiocarbonyl]ethyl]-1-[1-hydroxy-1-(pivaloyloxymethylloxycarbonyl)methyl]-2-azetidinone (preparation given) was treated with SOCl<sub>2</sub> and pyridine in THF at -40 to -50° and the resultant 1-[1-chloro-1-(pivaloyloxymethylloxycarbonyl)methyl] derivative was cyclized by Et<sub>3</sub>N in DMF at -20 to 0° to give (5R,6S,7R)-II [R1 = (R)-Me<sub>3</sub>CSiMe<sub>2</sub>OCHMe, R2 = CH<sub>2</sub>OCOCMe<sub>3</sub>, X =  $\beta$ -CHMe]. Desulfurization of this with KOCMe<sub>3</sub> and PPh<sub>3</sub> in PhMe at -40 to -20° and esterification by quenching in a solution of ClP(O)(OPh)<sub>2</sub> in MeCN gave (1R,5S,6S)-I [R1 = (R)-Me<sub>3</sub>CSiMe<sub>2</sub>OCHMe, R2 = CH<sub>2</sub>OCOCMe<sub>3</sub>, X =  $\beta$ -CHMe] [III; Y = OP(O)(OPh)<sub>2</sub>]. Treatment of this with (4S)-4-mercaptopyrrolidine-2-thione and (iso-Pr)<sub>2</sub>NEt in MeCN gave III [Y = (4R)-pyrrolidin-2-thion-4-ylthio]. A subset of I [i.e., R1 = MeCH(OR<sub>6</sub>); R2 as given; X = CHMe; Y = 1-R<sub>5</sub>-2-thioxopyrrolidinylthio; R<sub>5</sub> = H, alkyl, alkoxyalkyl, dialkylaminoalkyl; R<sub>6</sub> = H, protective group] are novel and show better antibacterial activity, stability to dehydropeptidase 1, oral absorbability, and toxicity in comparison to known analogs where Y is a 2-oxopyrrolidin-4-ylthio group.

RX(11) OF 52

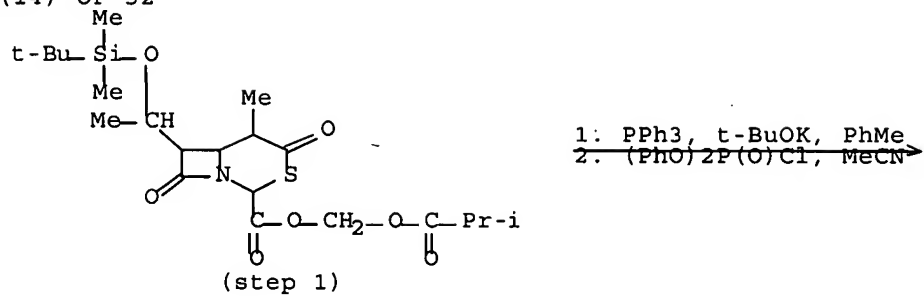


RX(11) OF 52

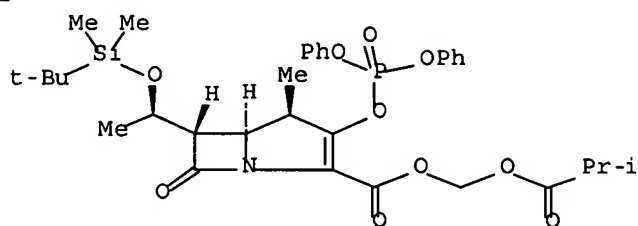


NOTE: -40 to -20.degree., then to 0.degree.

RX(14) OF 52

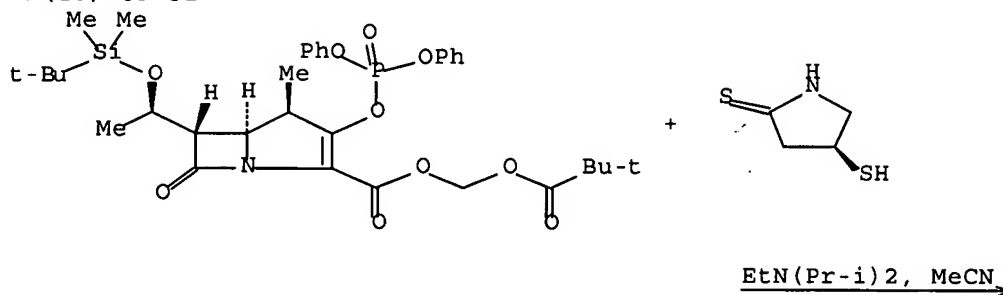


RX(14) OF 52

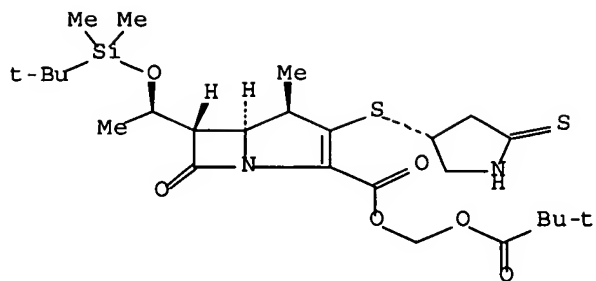


NOTE: -40 to -20.degree., then to 0.degree.

RX(16) OF 52

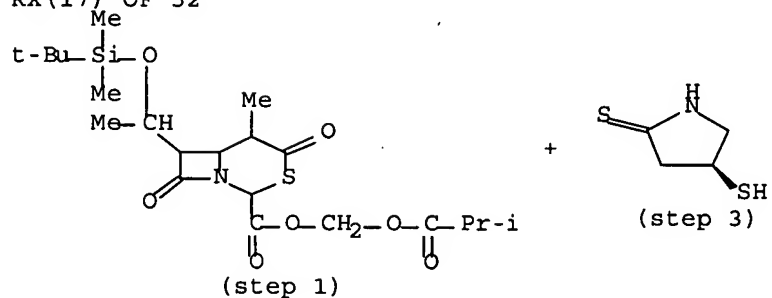


RX(16) OF 52

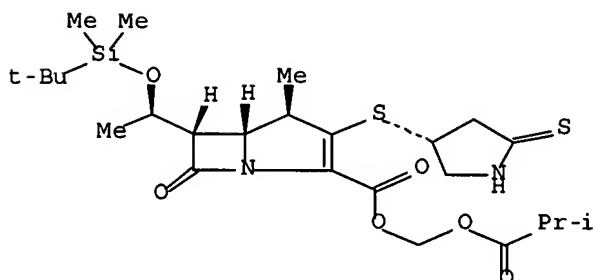


NOTE: -20 to 0.degree.

RX(17) OF 52

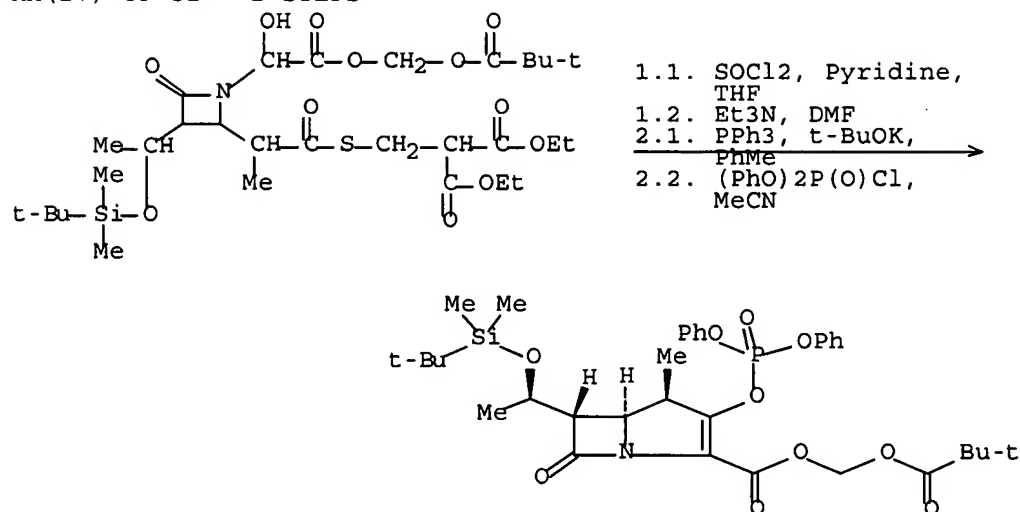


RX(17) OF 52



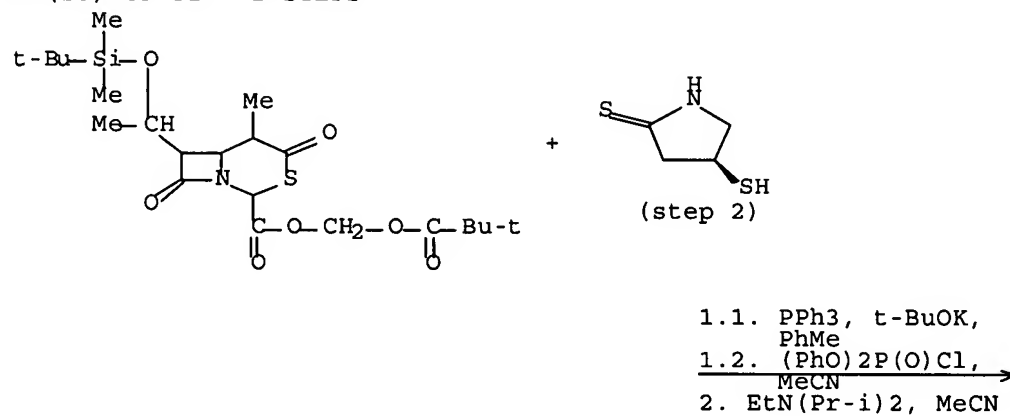
NOTE: -40.degree., then -40.degree., then -20 to -5.degree.

RX(27) OF 52 - 2 STEPS

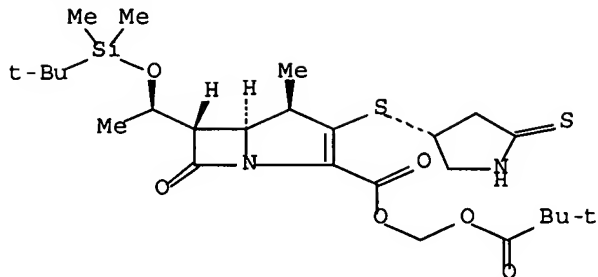


NOTE: 1)  $-50$  to  $-40$ .degree., then  $-20$  to  $0$ .degree., 2)  $-40$  to  $-20$ .degree., then to  $0$ .degree.

RX(28) OF 52 - 2 STEPS

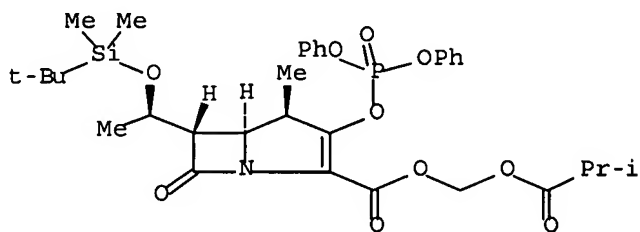
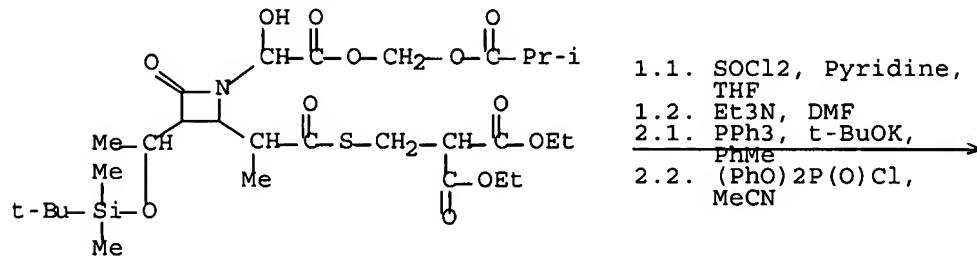


RX(28) OF 52 - 2 STEPS



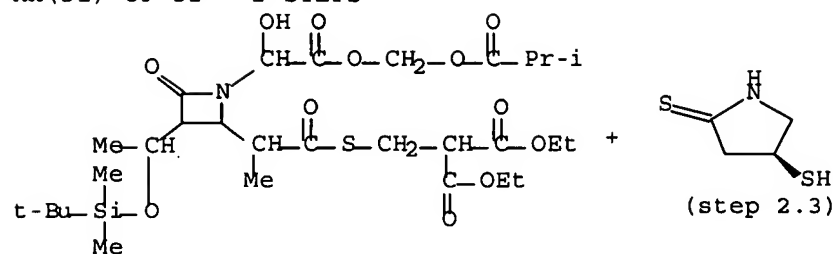
NOTE: 1) -40 to -20.degree., then to 0.degree., 2) -20 to 0.degree.

RX(30) OF 52 - 2 STEPS



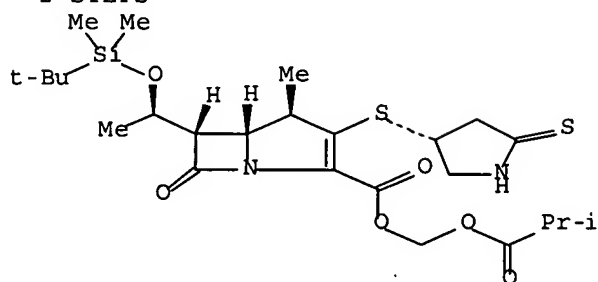
NOTE: 1) -50 to -40.degree., then -20 to 0.degree., 2) -40 to -20.degree., then to 0.degree.

RX(31) OF 52 - 2 STEPS



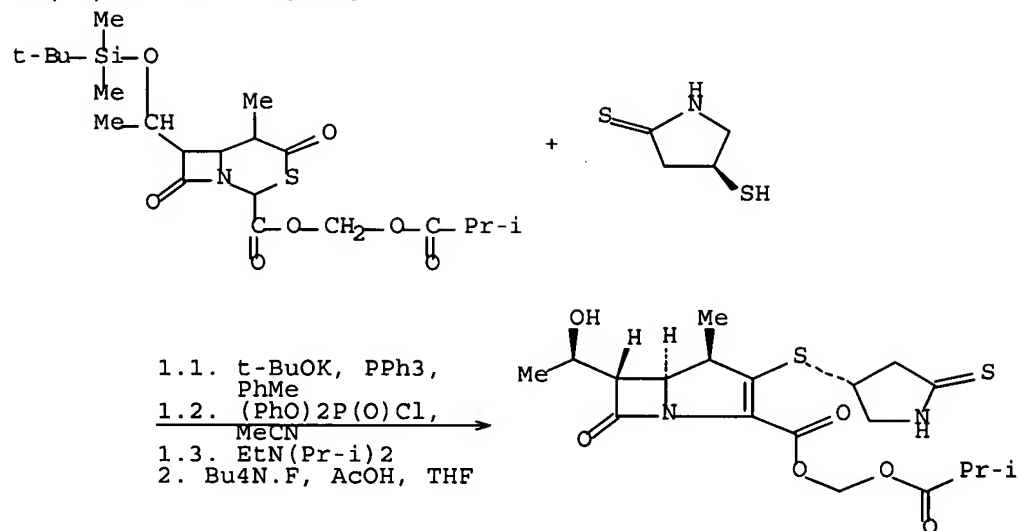
- 1.1. SOCl<sub>2</sub>, Pyridine,  
THF  
1.2. Et<sub>3</sub>N, DMF  
2.1. t-BuOK, PPh<sub>3</sub>,  
PhMe  
2.2. (PhO)<sub>2</sub>P(O)Cl,  
MeCN  
2.3. EtN(Pr-i)<sub>2</sub>

RX(31) OF 52 - 2 STEPS



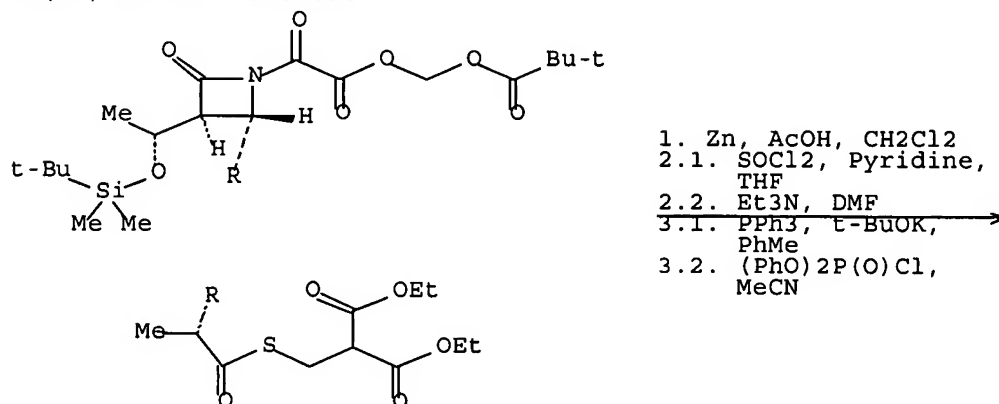
NOTE: 1) -50 to -40.degree., then -20 to 0.degree., 2) -40.degree.,  
then -40.degree., then -20 to -5.degree.

RX(32) OF 52 - 2 STEPS

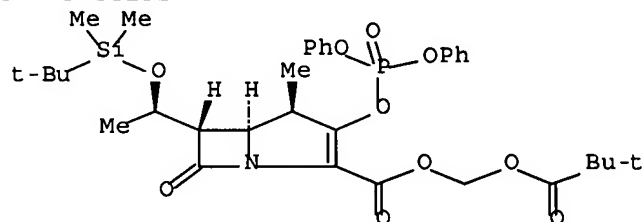


NOTE: 1) -40.degree., then -40.degree., then -20 to -5.degree., 2) room temp.

RX(41) OF 52 - 3 STEPS

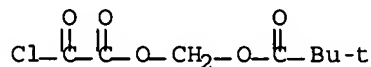
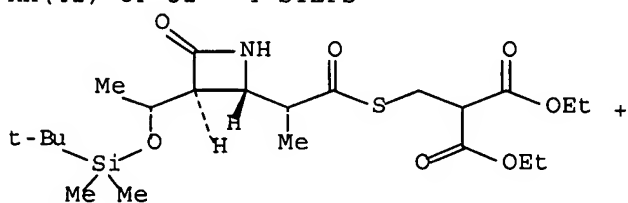


RX(41) OF 52 - 3 STEPS



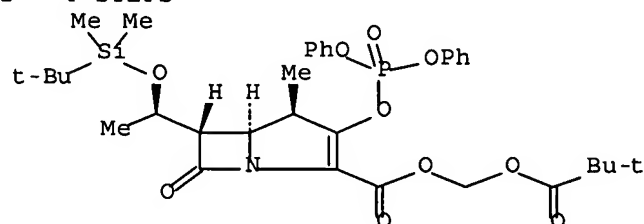
NOTE: 1) 0.degree., 2) -50 to -40.degree., then -20 to 0.degree., 3)  
-40 to -20.degree., then to 0.degree.

RX(42) OF 52 - 4 STEPS



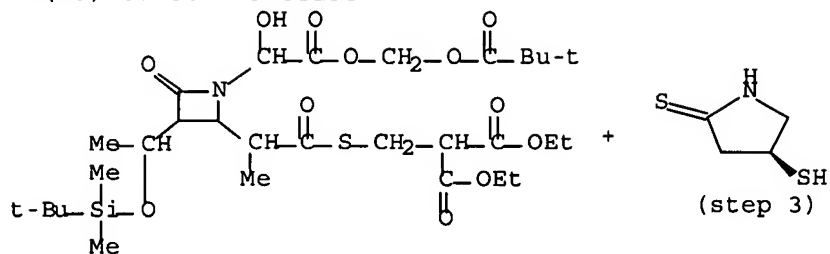
1. 2,6-Lutidine,  
4-DMAP, CH<sub>2</sub>Cl<sub>2</sub>
2. Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>
- 3.1. SOCl<sub>2</sub>, Pyridine,  
THF
- 3.2. Et<sub>3</sub>N, DMF
- 4.1. PPh<sub>3</sub>, t-BuOK,  
PhMe
- 4.2. (PhO)<sub>2</sub>P(O)Cl,  
MeCN

RX(42) OF 52 - 4 STEPS



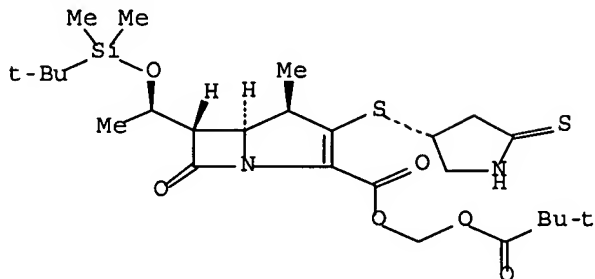
NOTE: 1) 0.degree., 2) 0.degree., 3) -50 to -40.degree., then -20 to  
0.degree., 4) -40 to -20.degree., then to 0.degree.

RX(43) OF 52 - 3 STEPS



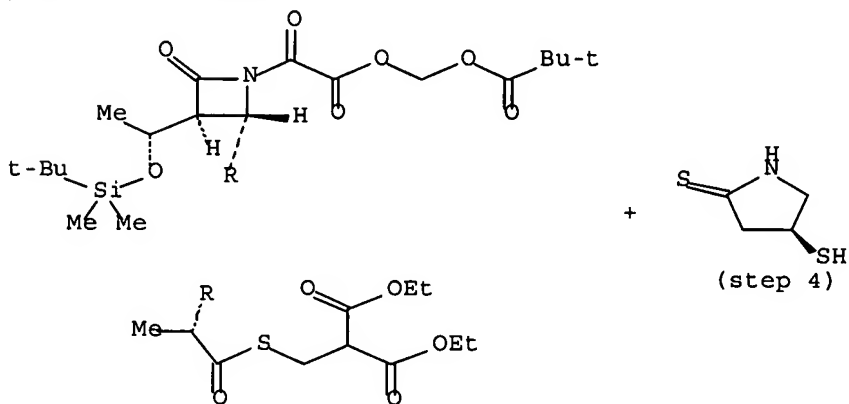
- 1.1. SOCl<sub>2</sub>, Pyridine,  
THF  
1.2. Et<sub>3</sub>N, DMF  
2.1. PPh<sub>3</sub>, t-BuOK,  
PhMe  
2.2. (PhO)<sub>2</sub>P(O)Cl,  
MeCN  
3. EtN(Pr-i)<sub>2</sub>, MeCN

RX(43) OF 52 - 3 STEPS



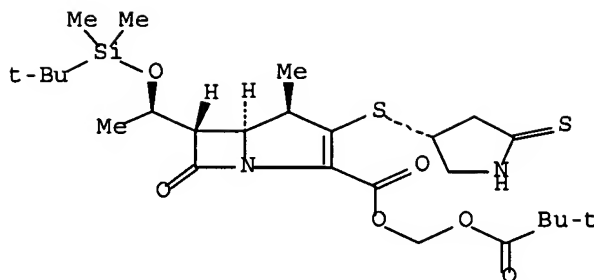
NOTE: 1) -50 to -40.degree., then -20 to 0.degree., 2) -40 to -20.degree., then to 0.degree., 3) -20 to 0.degree.

RX(44) OF 52 - 4 STEPS



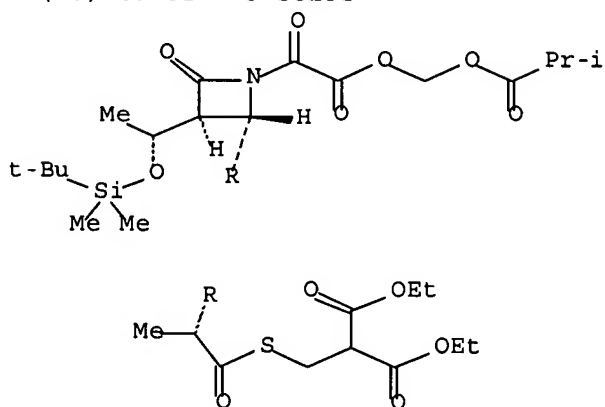
## RX(44) OF 52 - 4 STEPS

1. Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>
- 2.1. SOCl<sub>2</sub>, Pyridine,  
THF
- 2.2. Et<sub>3</sub>N, DMF
- 3.1. PPh<sub>3</sub>, t-BuOK,  
PhMe
- 3.2. (PhO)<sub>2</sub>P(O)Cl,  
MeCN
4. EtN(Pr-i)<sub>2</sub>, MeCN



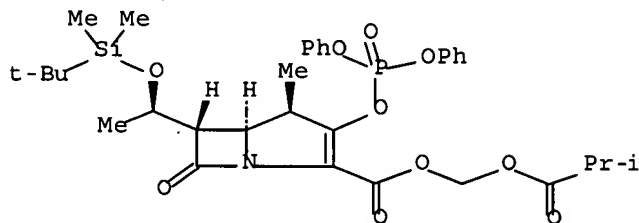
NOTE: 1) 0.degree., 2) -50 to -40.degree., then -20 to 0.degree., 3) -40 to -20.degree., then to 0.degree., 4) -20 to 0.degree.

## RX(45) OF 52 - 3 STEPS



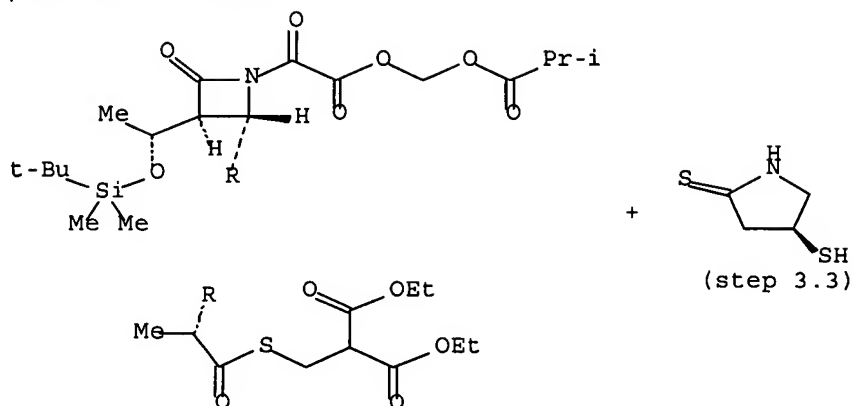
1. Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>
- 2.1. SOCl<sub>2</sub>, Pyridine,  
THF
- 2.2. Et<sub>3</sub>N, DMF
- 3.1. PPh<sub>3</sub>, t-BuOK,  
PhMe
- 3.2. (PhO)<sub>2</sub>P(O)Cl,  
MeCN

## RX(45) OF 52 - 3 STEPS



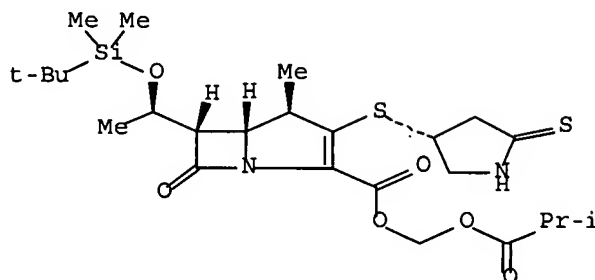
NOTE: 1) 0.degree., 2) -50 to -40.degree., then -20 to 0.degree., 3) -40 to -20.degree., then to 0.degree.

RX(46) OF 52 - 3 STEPS



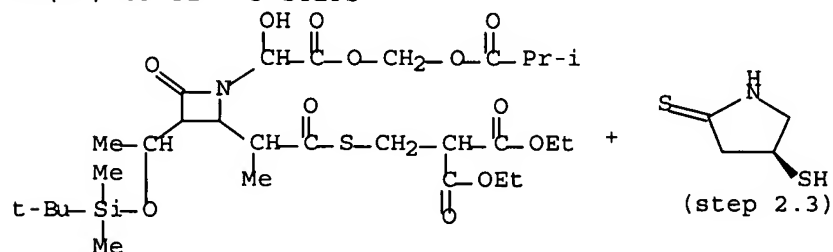
RX(46) OF 52 - 3 STEPS

1. Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>
- 2.1. SOCl<sub>2</sub>, Pyridine, THF
- 2.2. Et<sub>3</sub>N, DMF
- 3.1. t-BuOK, PPh<sub>3</sub>, PhMe
- 3.2. (PhO)<sub>2</sub>P(O)Cl, MeCN
- 3.3. EtN(Pr-i)<sub>2</sub>

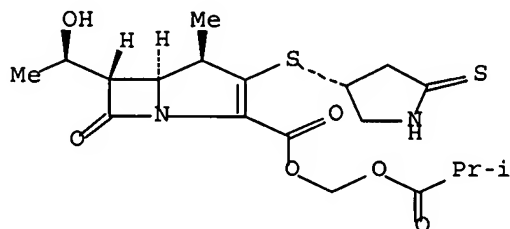


NOTE: 1) 0.degree., 2) -50 to -40.degree., then -20 to 0.degree., 3) -40.degree., then -40.degree., then -20 to -5.degree.

RX(47) OF 52 - 3 STEPS

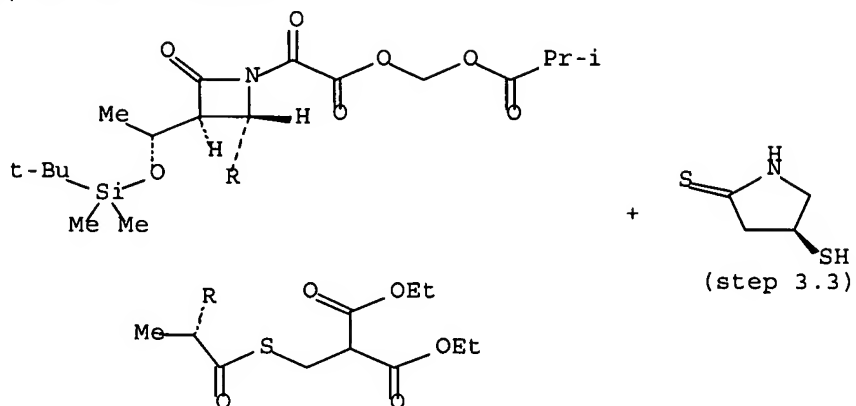


- 1.1. SOCl<sub>2</sub>, Pyridine, THF
- 1.2. Et<sub>3</sub>N, DMF
- 2.1. t-BuOK, PPh<sub>3</sub>, PhMe
- 2.2. (PhO)<sub>2</sub>P(O)Cl, MeCN
- 2.3. EtN(Pr-i)<sub>2</sub>
3. Bu<sub>4</sub>N.F, AcOH, THF



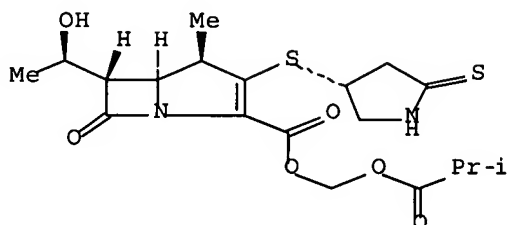
NOTE: 1) -50 to -40.degree., then -20 to 0.degree., 2) -40.degree., then -40.degree., then -20 to -5.degree., 3) room temp.

RX(48) OF 52 - 4 STEPS



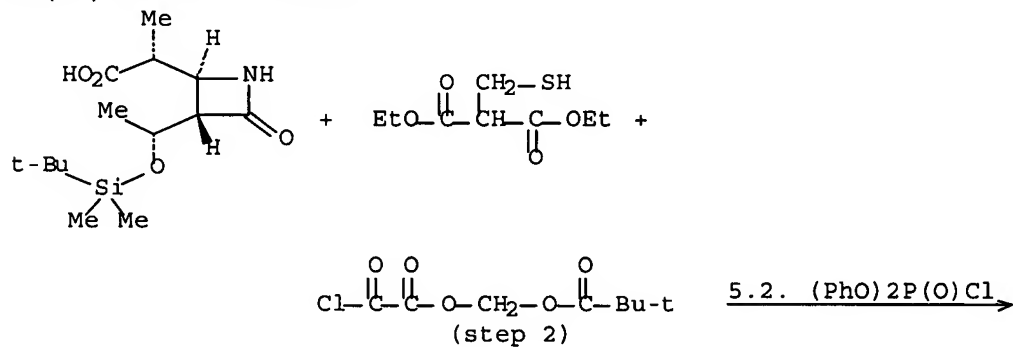
RX(48) OF 52 - 4 STEPS

1. Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>
- 2.1. SOCl<sub>2</sub>, Pyridine, THF
- 2.2. Et<sub>3</sub>N, DMF
- 3.1. t-BuOK, PPh<sub>3</sub>, PhMe
- 3.2. (PhO)<sub>2</sub>P(O)Cl, MeCN
- 3.3. EtN(Pr-i)<sub>2</sub>
4. Bu<sub>4</sub>N.F, AcOH, THF

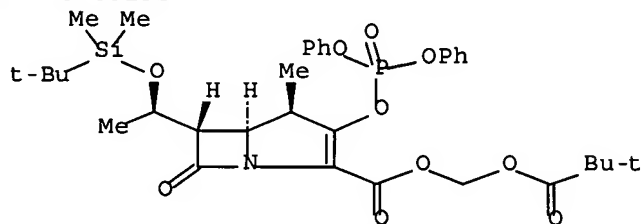


NOTE: 1) 0.degree., 2) -50 to -40.degree., then -20 to 0.degree., 3) -40.degree., then -40.degree., then -20 to -5.degree., 4) room temp.

RX(50) OF 52 - 5 STEPS

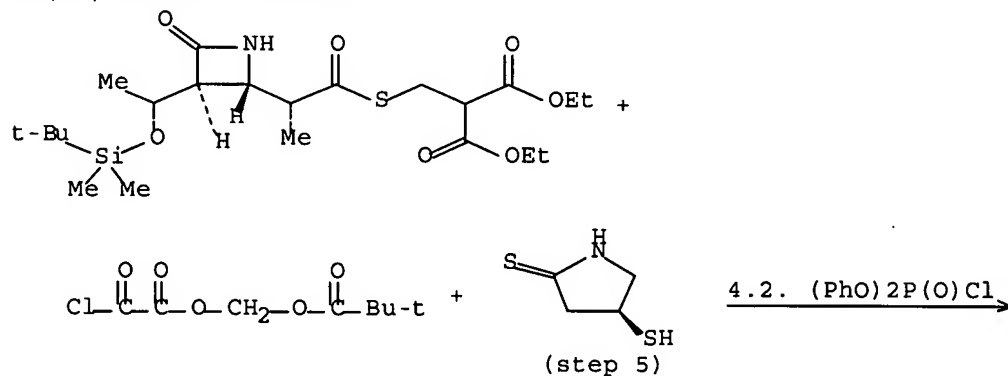


RX(50) OF 52 - 5 STEPS

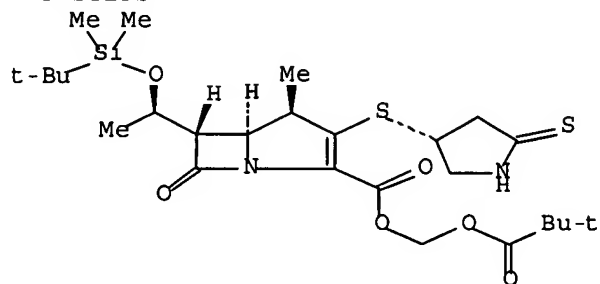


NOTE: 1) room temp., 2) 0.degree., 3) 0.degree., 4) -50 to -40.degree., then, -20 to 0.degree., 5) -40 to -20.degree., then to 0.degree.

RX(51) OF 52 - 5 STEPS

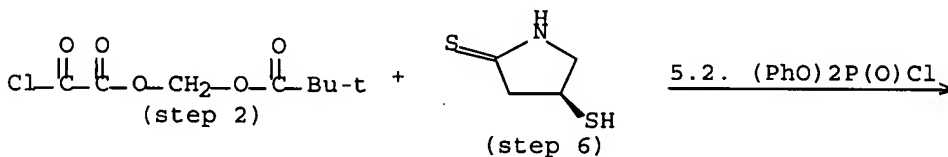
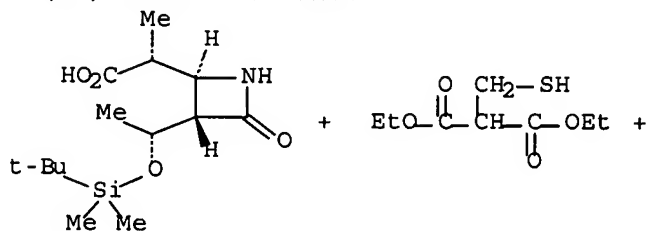


RX(51) OF 52 - 5 STEPS

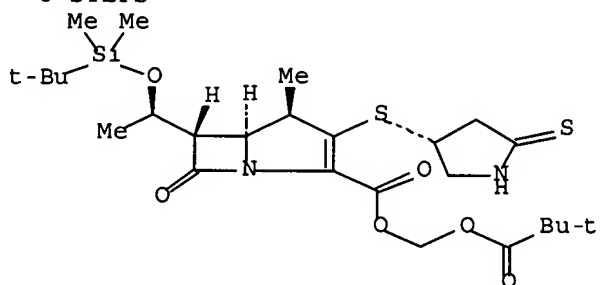


NOTE: 1) 0.degree., 2) 0.degree., 3) -50 to -40.degree., then -20 to 0.degree., 4) -40 to -20.degree., then to 0.degree., 5) -20 to 0.degree.

RX(52) OF 52 - 6 STEPS



RX(52) OF 52 - 6 STEPS



NOTE: 1) room temp., 2) 0.degree., 3) 0.degree., 4) -50 to -40.degree., then -20 to 0.degree., 5) -40 to -20.degree., then to 0.degree., 6) -20 to 0.degree.

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(FILE 'HOME' ENTERED AT 09:13:07 ON 15 JUN 2007)

FILE 'REGISTRY' ENTERED AT 09:13:21 ON 15 JUN 2007

FILE 'BEILSTEIN' ENTERED AT 09:13:25 ON 15 JUN 2007  
L1 STR

FILE 'CASREACT' ENTERED AT 09:16:18 ON 15 JUN 2007

L2 0 SEA SSS SAM L1 ( 0 REACTIONS)  
L3 0 SEA SSS FUL L1 ( 0 REACTIONS)  
D QUE  
D COST

FILE 'CAPLUS' ENTERED AT 09:18:20 ON 15 JUN 2007

E US2005-533183/APPS  
L4 1 SEA ABB=ON PLU=ON US2005-533183/AP  
SEL RN

FILE 'REGISTRY' ENTERED AT 09:18:50 ON 15 JUN 2007

L5 18 SEA ABB=ON PLU=ON (100-39-0/BI OR 105318-28-3/BI OR 157429-42  
-0/BI OR 157542-49-9/BI OR 161715-24-8/BI OR 179337-57-6/BI OR  
18997-19-8/BI OR 2524-64-3/BI OR 682747-73-5/BI OR 692779-22-9/  
BI OR 692779-23-0/BI OR 692779-24-1/BI OR 692779-25-2/BI OR  
692779-26-3/BI OR 7087-68-5/BI OR 74-88-4/BI OR 75-77-4/BI OR  
994-30-9/BI)  
D SCA  
L6 STR L1

FILE 'CASREACT' ENTERED AT 09:24:41 ON 15 JUN 2007

L7 0 SEA SSS SAM L6 ( 0 REACTIONS)  
L8 4 SEA SSS FUL L6 ( 90 REACTIONS)  
D SCA

FILE 'CASREACT' ENTERED AT 09:25:21 ON 15 JUN 2007

FILE 'CASREACT' ENTERED AT 09:25:29 ON 15 JUN 2007  
D QUE L4

FILE 'CASREACT' ENTERED AT 09:25:39 ON 15 JUN 2007  
D QUE L8

FILE 'CASREACT' ENTERED AT 09:25:59 ON 15 JUN 2007  
D QUE L3  
D QUE L8  
D L8 IBIB ABS CRD TOT